HETEROLYTIC CLEAVAGE OF COBALT—CARBON BOND IN ORGANOCOBALOXIMES : A MECHANISTIC STUDY

A Thesis Presented

by

MANOJ KUMAR

to

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for the Degree of

DOCTOR OF PHILOSOPHY

in the Subject of

CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY

KANPUR, INDIA

JULY, 1987

Dedicated

To

My Parents

Dedicated

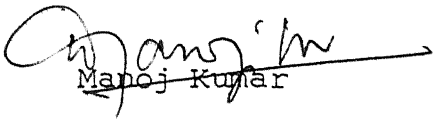
To

My Parents

STATEMENT

I hereby declare that the matter embodied in this thesis "Heterolytic Cleavage of Cobalt-Carbon Bond in Organocobaloximes: A Mechanistic Study" is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Professor B.D. Gupta.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators. The author is responsible for purely unintentional oversights and errors which could be traced herein.



Manoj Kumar

Kanpur:
July 20, 1987

CERTIFICATE

Certified that the work "Heterolytic Cleavage of Cobalt-Carbon Bond in Organocobaloximes: A Mechanistic Study" presented in this thesis, has been carried out by Mr. Manoj Kumar, under my supervision and the same has not been submitted elsewhere for a degree.

(B.D. GUPTA)
Thesis Supervisor
(Assistant Professor)
Dept. of Chemistry,
I.I.T.-KANPUR

Kanpur:
July 20, 1987

DEPARTMENT OF CHEMISTRY,
INDIAN INSTITUTE OF TECHNOLOGY, KANPUR, INDIA

CERTIFICATE OF COURSE WORK

This is to certify that Mr. Manoj Kumar has satisfactorily completed all the course requirements for Ph.D. degree programme in Chemistry. The course include:

Chm 505 Principles of Organic Chemistry

Chm 524 Modern Physical Methods in Chemistry

Chm 525 Principles of Physical Chemistry

Chm 541 Advanced Inorganic Chemistry I

Chm 545 Principles of Inorganic Chemistry

Chm 646 Bioinorganic Chemistry

Chm 800 General Seminar

Chm 801 Graduate Seminar

Chm 900 Post-Graduate Research

Mr. Manoj Kumar has successfully completed his Ph.D. written and oral qualifying examinations and was admitted to the candidacy of the Ph.D. degree August 10, 1983.

P. K. Goel

(P.S. Goel)
Professor and Head
Department of Chemistry
I.I.T.-KANPUR

(S. Sarkar)
Convener,
Departmental Post-Graduate
Committe, Dept. of Chemistry,
IIT- KANPUR

PREFACE

Transition metals are known to have a marked effect on the reactions of organic molecules to which they are π bonded. However, much less is known about the influence of σ bonded transition metals on organic reactivity, both in degree and direction. Study of mechanism provides a valuable information about ways in which carbon-metal bond is cleaved. Organobis-(dimethylglyoximato)pyridine-cobalt(III), trivially known as organocobaloximes is one such class of σ bonded compounds and are accepted as the model compounds of vitamin B_{12} coenzyme. Though an enormous amount of study has been done on these systems, to understand the diverse chemistry of vitamin B_{12} coenzyme, the chemistry of organocobaloximes, in the recent years, has emerged as an independent area comprising of many novel class of organometallic reactions which originate from the cleavage of Co-C σ bond. The study of mechanism through which Co-C bond is cleaved and the factors that promote (or inhibit) such cleavage, are of considerable importance. This aim of work results in the thesis entitled: " Heterolytic Cleavage of Cobalt-Carbon Bond in Organocobaloximes: A Mechanistic Study " and deals mainly with the organometallic aspects of organocobaloximes, however, the results may find an indirect implications on the chemistry of vitamin B_{12} coenzyme.

In the first chapter of the thesis a comprehensive and uptodate account of organocobaloxime chemistry has been taken

up with a particular emphasis on the stability of Co-C bond, synthesis and the reactions of such compounds.

Since halogens as electrophiles are effective reagents for the displacement of an organic group σ- bonded to cobalt, the reactions of halogens with benzyl cobaloximes in chloroform or acetic acid under anaerobic and dark conditions comprise the second chapter. All reactions are carried out under conditions where the concentration of halogen is kept very low so that the reactions of higher order in halogen are negligible. In the first part of this chapter, the cobaloximes, $4\text{-}RC_6H_4CH_2Co^{III}(dmgH)_2Py$ (R = H, Me, $CHMe_2$, CMe_3, Cl, Br, CN, CHO, COOH, NO_2) are taken up for study. Organic halides are the exclusive organic products formed when R = Me, $CHMe_2$, CMe_3 whereas a mixture of products including $4\text{-}RC_6H_4CH_2X$ and benzyl ethers of dimethylglyoxime ($4\text{-}RC_6H_4CH_2\text{-}ON{=}CMe\text{-}CMe{=}NOH$) are observed in varying amounts when R = Cl, Br, CN, CHO, COOH, NO_2. Apart from the direct electrophilic mechanism, the participation of oxidative dealkylation mechanism is conclusively proved by many independent experiments.

In order to see whether the effect of substituent in the benzene ring is transmitted to the Co-C bond, and whether such an effect is inductive or mesomeric in nature, the second part of this chapter aims at the study of organocobaloximes $4\text{-}RC_6H_4CH_2Co^{III}(dmgH)_2Py$ (R = $NHCOCH_3$, NMe_2, OCH_3). Both ring halogenated and Co-C cleavage products are formed when R = $NHCOCH_3$

and NMe_2, however, ring substituted toluene (2-halo-4-methoxy-toluene) is the exclusive organic product formed when R = OMe. Besides, the Co-C bond reactivity is so much faster in these cases that it almost approaches the encounter rate. A direct electrophilic mechanism is envisaged and the transmission of the substituent effect on to Co-C bond is found to be mesomeric in nature. A further conclusive evidence in support of the latter comes from the halogenation study of organocobaloximes of the type $PhXCH_2Co^{III}(dmgH)_2Py$ (X = O, S, NH) which forms the third part of the second chapter. It is proved beyond doubt, that the substantial ring halogenation in these systems results due to the activating effect of the heteroatom as well as the $-CH_2Co^{III}(dmgH)_2Py$ group. Moreso, the activating effect of the latter is transmitted to the aromatic ring via the heteroatom only and such a transmission occurs by σ-π conjugation mechanism In the fourth part of this chapter, the effect of meta-substitution into the benzene ring is taken up. Hence, the halogenation of $3\text{-}RC_6H_4CH_2Co^{III}(dmgH)_2Py$ (R = Me, OMe) indicates that the meta-substitution is much more effective towards ring activation as compared to the para-substitution. Similarly, the effect of protonation and BF_2 bridging of the equatorial dimethylglyoximato ligands in para-substituted benzyl cobaloxime is studied which points to the observation that the Co-C bond is weakened in these compounds.

In the above studies, it is observed that although the reaction conditions do not allow the participation of a direct

free radical pathway, but induced free radical process definitely comes into play as a consequence of oxidative dealkylation process. Since the final product i.e., the organic halide obtained is same as that from the direct electrophilic or oxidative dealkylation process, the relative contribution of the induced free radical process can not be accurately assessed. Hence, in the third chapter, the study of benzyl cobaloximes with thiocyanogen is undertaken since both organothiocyanates and organoisothiocyanates will form in the free radical reaction The reactions of benzyl cobaloximes, $4\text{-}RC_6H_4CH_2Co^{III}(dmgH)_2Py$ (R = H, Me, OMe, Cl, CN, NO_2) with thiocyanogen form a variety of products including thiocyanates, isothiocyanates, bibenzyls and benzyl ethers of dimethylglyoxime. It is proved, beyond doubt, that five coordinate benzyl cobaloxime (after pyridine loss) is the reactive species in all these reactions and once again, oxidative dealkylation is a predominant process in such reactions.

Publications

1. Halogenolysis of para-substituted benzyl cobaloximes,
   B.D. Gupta and Manoj Kumar,
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*2. Oxidation of benzyl cobaloximes by manganese(III) acetate,
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*3. Homolytic substitution at saturated carbon centre: Synthesis of benzyl sulphones,
   B.D. Gupta, Manoj Kumar, Indira Das and M. Roy,
   Tetrahedron Letts., 27, No. 47 (1986) 5773-5776.

4. Halogenolysis of organocobaloximes: Ring substitution versus Co-C bond cleavage,
   B.D. Gupta and Manoj Kumar,
   Chemistry Letter (1987) 701-704.

5. Activation of electrophilic aromatic substitution by $CH_2Co(dmgH)_2Py$,
   B.D. Gupta and Manoj Kumar,
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6. Halogenation of organocobaloximes: Activation of electrophilic aromatic substitution by $CH_2Co^{III}(dmgH)_2Py$ group,
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   Proceedings XIIth International Conference on Organometallic Chemistry, held in Vienna, Sept. 8-13, 1985, p. 172 (Austria).

*Not included in the thesis.

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Publications (contd.)

6. Heterolytic cleavage of Co-C bond by thiocyanogen in benzyl cobaloximes,
   Manoj Kumar and B.D. Gupta,
   J.C.S., Chem. Commun. (communicated).

7. Ring substitution versus Co-C cleavage in organocobaloximes $PhYCH_2Co^{III}(dmgH)_2Py$ (Y = O, S, NH),
   B.D. Gupta and Manoj Kumar,
   (to be communicated).

8. Halogenation of benzyl, heteroaromatic methyl and C bonded methylene Y phenylcobaloximes (Y = O, S, NH): A direct competition between ring halogenation and Co-C bond cleavage,
   Manoj Kumar, B.D. Gupta and Sujit Roy,
   (manuscript under preparation)

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MANOJ KUMAR

CONTENTS

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Chapter 1

ORGANOCOBALOXIMES: A MULTIFACET SYSTEM:
Classical σ bonded organometallic, Potential synthetic organic precursor, Model for B_{12}.

Introduction

Organometallic chemistry is the border area between the classical subdivision of organic and inorganic chemistry. Four major components of this area are:

a) compounds in which metal and carbon are linked by σ bonds,

b) metal carbonyls and their derivatives,

c) compounds in which unsaturated organic molecules are bonded to metals through π-bonds, and

d) compounds in categories (a-c) showing biological activity and effect.

The organometallic chemistry advents back to 18th century when tetramethyldiarsine was obtained as a byproduct in the photolysis of cobalt ore smaltite.[1] It took almost hundred years to characterise the compound.[2] Frankland in 1849 isolated

and characterised diethylzinc - the first ever organometallic compound with metal to ligand σ bond.[3] On the other hand, the first olefin-metal compound, the Zeise's salt was reported in 1827.[4,5]

With the turn of this century, organometallic chemistry has seen an enormous growth with a special significance to catalytic properties and organic synthesis. The names of Grignard, Gilman, Ziegler, Wilkinson, Mond, Rochow and many other workers are very significant with their great contribution to organometallic chemistry. Their work has been very well documented and reviewed in literature.[6-15]

During the last three decades or so, the study of organometallic chemistry has grown rapidly. Expansion of this area of endeavour has been fostered by the discovery of several classes of compounds including alkali, alkaline-earths, transition and transuranium metals.

1.1 Co-C Bond: A Period of Dormancy

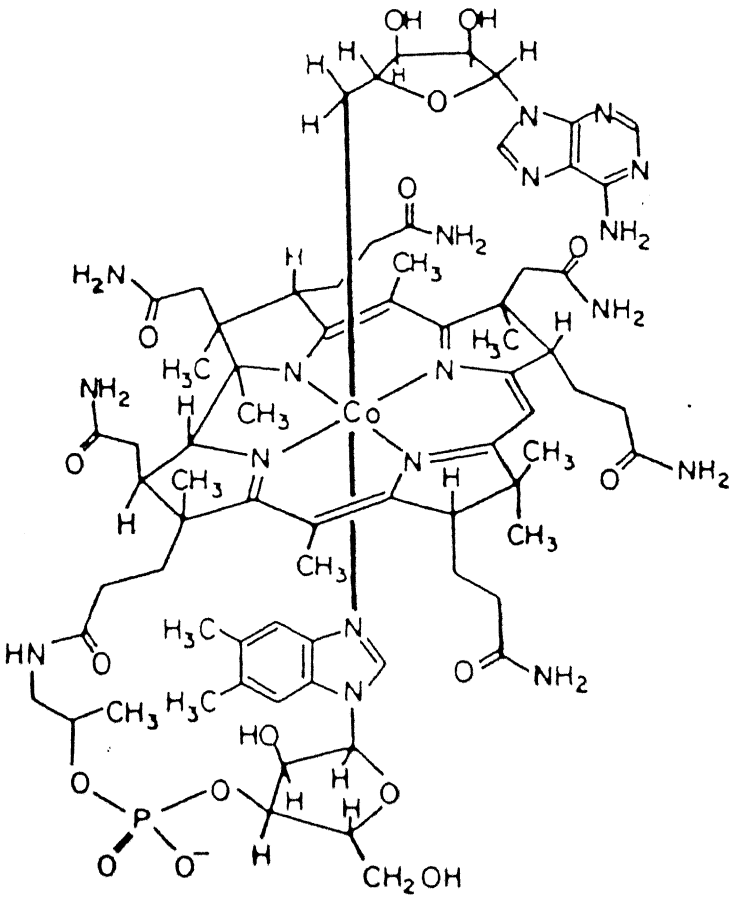
Upto the middle of this century, the field of organocobalt chemistry was limited to a group of ill-defined alkyl and aryl-compounds.[16] The reported complexes were either not fully characterised or they were obtained in very poor yields. Above all they were extremely unstable. However, with the great expansion of organometallic chemistry in the late 1950's and aided by the knowledge that carbon to transition metal bond

might be stabilized by certain ligands, there was also some progress into the preparation of compounds containing Co-C bond.[17] Dialkyl cobalt, used commercially as an additive in drying oils, may be considered as the first stable complex of cobalt.[18] Complexes of empirical formula $RCoX_n$ (R = α,β-naphthyl; X = Br, I) have been prepared but partially characterized by Ingles and Polya.[19] Besides, a few acetylide complexes,[20] aryl complexes,[21] partially or fully characterized, and isolated in very poor yields have also been reported in literature.[22,23]

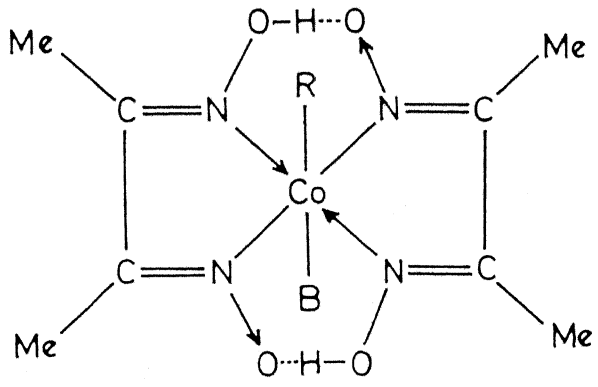
It has now become very obvious that the σ bonded organometallic compounds of main group elements and transition metals contribute a diverse and rich field of research. However, organo-cobalt chemistry especially that of Co-C sigma bond was still in the embryonic stage and could not be enlightened to a similar degree even by the middle of this century.

1.2 From Nature's Basket

At a time when σ bonded organocobalt chemistry was passing through a dormant phase, in 1962 came one of the most interesting developments that have occurred so far in organometallic chemistry. This was the discovery following brilliant and elegant X-ray crystallographic study of vitamin B_{12} by Galen Lenhert and Dorothy Hodgkin from Oxford, that a naturally occurring molecule, vitamin B_{12} coenzyme, contained a cobalt-



Coenzyme B_{12}



Organocobaloxime

Fig. 1 Reproduced from ref. 116 .

carbon bond.[24] It was for the first time that a naturally occurring transition metal organometallic compound was recognized and was one of the most stable sigma bonded organocobalt compound ever reported. The contemporary chemical studies showed that this bond was unaffected by a number of reagents which cleaved bonds elsewhere in the molecule.[25] The structure of vitamin B_{12} coenzyme (Fig. 1) points out the following salient features:

a) an axial Co-C σ bond between cobalt and the ribosyl portion of Adenosyl group,

b) an equatorial ring structure comprising of four donor nitrogen atoms from pyrrole groups of the macrocyclic corrin ring,

c) an axial base ligand, normally a derivative of benzimidazole.

The above features are common to all vitamin B_{12} derivatives, but with changes in axial ligands bound to cobalt. In general, all molecules exhibiting the tetrapyrrole corrin ring structure are referred to as corrinoids. When the base ligand is an α-5,6-dimethylbenzimidazole nucleotide as in Fig. 1, the molecule is termed as cobalamin. Although majority of the B_{12} derivatives are diamagnetic (disregarding a small amount of temperature independent paramagnetism) with cobalt in +3 oxidation state, other lower oxidation states of cobalt also exist. The derivatives with +1 and +2 states are referred to as

vitamin B_{12s} and vitamin B_{12r}, respectively.

The realisation of the fact that vitamin B_{12} coenzyme, formally a complex of cobalt(III) and the corrin ring might be an important factor in the stabilization of Co-C bond, led to a wide consideration of the possibility that other carbon-cobalt(III) compounds might be formed with the same or analogous ligands. These ideas[26,27] led the synthetic inorganic chemists to the synthesis of a large number of σ bonded organocobalt complexes.

1.3 Co-C σ Bond: Synthesis Begins...

The problems faced by chemists in synthesizing stable compounds with Co-C bond started fading away in early sixties following studies related to cobalamin derivatives.[28] Many cobalamin derivatives were prepared. The progress in organocobalamins stimulated interest in the preparation and study of other organocobalt complexes and the year 1964 may be designated as a landmark in this field with the name of G.N. Schrauzer who reported a number of organobis(dimethylglyoximato)cobalt complexes, later known as cobaloximes.[29] It was soon established that the stability of Co-C bond virtually depended upon significantly and optimally strong, essentially planar ligand field. Moreover, the coordinating atom need not be nitrogen every time. Today a wide variety of such equatorial ligand systems are known that ranges from aromatic porphyrins[30] to the

completely saturated [14]-ane N_4 systems[31] with more than two thousand and five hundred organocobalt complexes in literature. The driving force behind these works has been the attempt to elucidate the mechanism of the B_{12}-dependent enzymatic reactions by studying the reactions of model compounds. However, it must be emphasized that because of their biochemical relevance to vitamin B_{12} coenzyme, cobaloximes were the most studied ones.[32]

1.3.1 General Methods of Synthesis of Organocobalt Complexes

Organocobalt complexes have been prepared by a large number of ways. The preparative methods include a greater choice than is usual in organometallic chemistry. These complexes offer interesting challenges to an organometallic chemist to apply new reagents and reactions and to study compounds, which are generally stable to both air and moisture. Many reviews have explored the preparative methods.[33-40] The methods of preparations are conveniently classified into the following main categories (Table 1.1).

A. Reaction of (Co^{I}) or Co-hydride species with electrophilic reagents.
B. Reaction of (Co^{II}) reagents with free radicals.
C. Reaction of (Co^{III}) complexes with nucleophiles.
D. Modification of an organocobalt complex.

Table 1.1. Summary of Methods of Preparation of Organocobalt(III) Complexes

Section	Inorganic reagent	Organic substrate	Products
A.1	(Co^{I})	RX; X = halide, tosylate etc.	$R(Co^{III}) + X^{-}$
	(Co^{I})	$R\overline{CHCH_2X}$; X = O, NH etc.	$RCHOHCH_2(Co^{III})$
	(Co^{I})	XCH=CHPh; X = Br, Cl	$PhCH=CH(Co^{III}) + X^{-}$
	(Co^{I})	$XCH=CH_2$; X = CN etc.	$XCH_2CH_2(Co^{III})$
	(Co^{I})	XC≡CH; X = Ph etc.	$XCH=CH(Co^{III})$
A.2	$H(Co^{III})$	$RCH=CH_2$	$MeCHR(Co^{III})$
	$H(Co^{III})$	RC≡CH	$CH_2=CR(Co^{III})$
	$H(Co^{III})$	$PhNH_2/HCHO$	$pHNHCH_2(Co^{III}) + H_2O$
B.	(Co^{II})	RX; X = halide	$R(Co^{III}) + X(Co^{III})$
	(Co^{II})	$RNHNH_2/O_2$	$R(Co^{III}) + N_2 + H_2O$
	(Co^{II})	$RCMe_2OOH$	$R(Co^{III}) + OH(Co^{III}) + Me_2CO$
C.	$X(Co^{III})$; H = halide	RM; M = metal	$R(Co^{III}) + MX$
	$X(Co^{III})$; X = halide	$CH_2=CHOR/ROH$	$(RO)_2CHCH_2(Co^{III})$
	$RO(Co^{III})$	R^1CH_3; R^1 = CN etc.	$R^1CH_2(Co^{III}) + ROH$
D.	$RO_2CCH_2(Co^{III})$ + OH^-/H^+	-	$HO_2CCH_2(Co^{III})$
	$HOCH_2CH_2(Co^{III})$ + $Ac_2O/ROH/RCO_2H$	-	$XOCH_2CH_2(Co^{III})$; X = Ac, R, CO_2R

A.1 From (Co^{I}) complexes

By far this is the most versatile route to organocobalt(III) complexes which involves the nucleophilic attack of a (Co^{I}) anionic species at the electrophilic centre of an alkylating reagent (RX),[33]

$$(Co^{I}) + RX \longrightarrow (Co^{III})\text{-}R + X^{-}$$

where R may be alkyl, benzyl, allyl, acyl, alkenyl, alkynyl etc., while X^{-} may be Cl^{-}, Br^{-}, I^{-}, tosylate and less commonly carboxylate, sulphate, phosphate, anhydride, trimethylamine and even mercury metal or nitrogen of diazomethane. The success of this method lies in the extremely high nucleophilic reactivity of (Co^{I}) species.[41-45] The Pearson nucleophilicity of (Co^{I}) derived from cobalamin and its model compounds lie within the range 14.0 ± 0.5 which is many-fold higher than those of conventional nucleophiles like CN^{-} (6.70) and I^{-} (7.42). (Co^{I}) is generally termed as supernucleophile.[42]

The attack of (Co^{I}) species at a saturated carbon centre of the ring system, for example, epoxides, ethyleneimine, THF and β-lactone effects ring opening[46]

$$(Co^{I}) + Me\text{-}\overbrace{CH_2\text{-}CH_2\text{-}O}^{} \longrightarrow Me\text{-}CHOHCH_2(Co^{III})$$

The reaction proceeds for cobalamins and cobaltoctaethyl porphyrin ring systems as well.[47] In an interesting variation,

the alkenyl cobaloxime, $[(p\text{-}ClC_6H_4)_2C{=}(Cl)C]Co^{III}$ is formed by the reaction of (Co^{I}) with (p,p'-DDT), a fully saturated molecule.[48]

It is noteworthy that the reductive arylation of (Co^{I}) with aryl halide has achieved little success so far. The yields of R-Co^{III} are being very poor.[49] Similarly, the reaction of vicinal dihalides yield acetylenes but no organocobalt(III) derivatives.[36]

Cobalt(I) species is generated by,

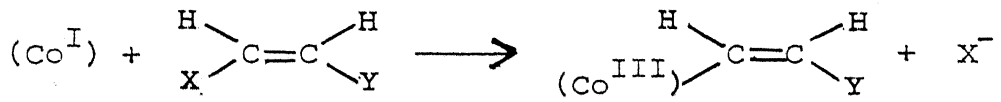
i) reduction of (Co^{II}) or (Co^{III}) reagents by sodium borohydride in alkaline medium,

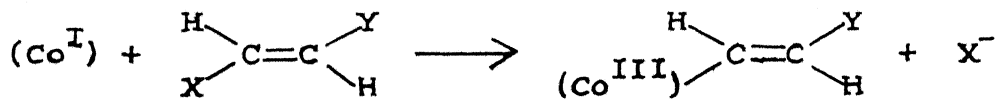
ii) disproportionation of (Co^{II}) to (Co^{III}) and (Co^{I}) in highly alkaline medium, and

iii) reduction of (Co^{II}) by hydrogen in acidic, neutral as well as in alkaline medium.

Reduction of (Co^{III}) chelates other than cobaloximes is done by sodium, potassium metals or their amalgams. For cobaloximes, method (i) and (ii) mentioned above, are employed most. However, fo the base sensitive alkylating agents method (iii) is found to be most effective. The reduction is generally carried out at temperatures below $0^{o}C$ under inert atmosphere of nitrogen or argon and is visibly sharp - a brown (Co^{II}) complex changing over to green to blue (Co^{I}) species.

The reaction of (Co^{I}) with substrate RX may occur either via an S_N2 or an electron transfer mechanism,[39] depending upon the conditions and reagent used. Several kinetic studies on the alkylation of (Co^{I}) by alkyl halides have established a bimolecular nucleophilic displacement mechanism for such systems.[42] Further proof for the mechanism comes from the observed inversion of configuration at the displacement centre of the alkyl halide in a number of cases.[50-52] However, several exceptions to S_N2 mechanism have been reported, e.g., with allylic halides both S_N2 and S_N2' mechanisms have been observed. From the kinetic studies on the reaction of substituted vinyl halides with (Co^{I}); Gaudemer et al. have suggested that the reaction proceeds via concerted displacement at sp^2 carbon, with retention of configuration about the double bond.[53,54]

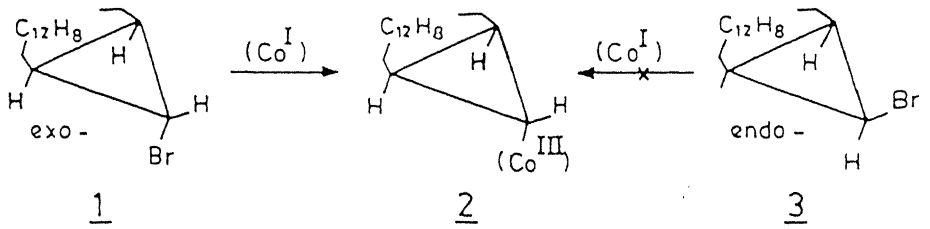




(X = Br, Cl; Y = C_6H_5, $CH_3CH_2COO^-$)

Recently, electron transfer mechanism has been proposed in number of cases.[55-59] Thus, the reaction of (Co^{I}) with different isomers of sterically hindered bromides (1, 3, 4) reveal

Scheme 1.1



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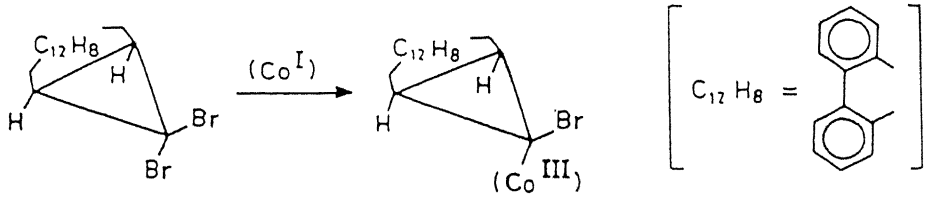

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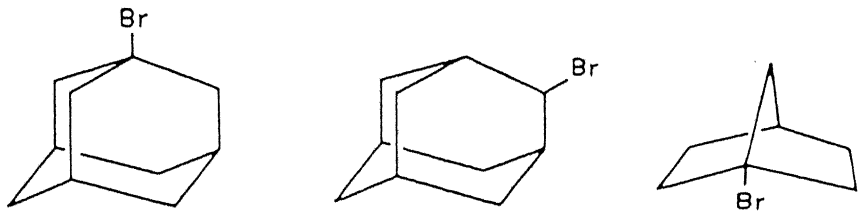

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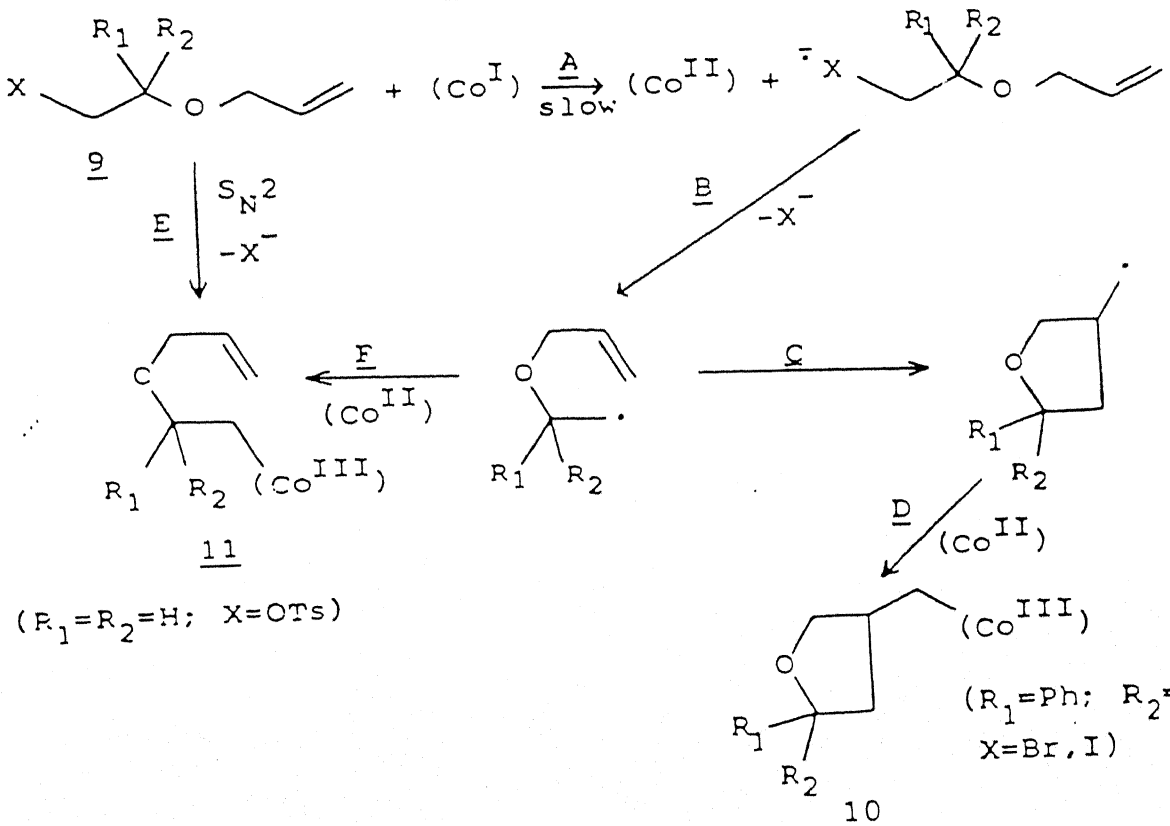
SCHEME 1.2



that only exo-structures, 1 and 4 yield the corresponding cobaloximes 2 and 5, while the endo-analogue 3 remains unreactive (Scheme 1.1).[55] An electron transfer mechanism has been proposed for these reactions, the retention being a consequence of shielding by dihydrophenanthrene moiety. A retentive alkylation of (Co^{I}) has also been reported with the sterically hindered halides 6 to 8 (Scheme 1.1).[56]

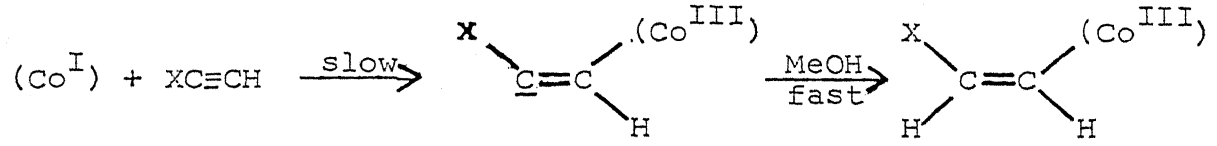
A conclusive evidence for the electron transfer mechanism has recently been reported by Tada et al. in the reaction of 2-(allyloxy)ethylhalide with (Co^{I}).[59] The mechanism is outlined in (Scheme 1.2). 2-(Allyloxy)ethyl halide 9 having substituent at β position ($R^1 \neq H$) givesonly the cyclized cobaloxime 10 via the electron transfer routes A, B, C and D. The corresponding reaction of 9 ($R^1 = R^2 = H$; X = tosylate) gives exclusively the direct substitution product 11 by an S_N2 mechanism (Route E). However, the formation of a mixture of 10 and 11 from 9 ($R^1 = R^2 = H$; X = Br, I) suggests the operation of both the processes simultaneously and even a new route F where (Co^{II}) capture by the organic radical takes place.

Besides the substitution reaction, cobalt(I) reagents add to unsaturated electrophiles, for example, it rapidly reacts with acrylonitrile and other such activated alkenes to give π-complexes which then slowly rearrange to the β-substituted cobaloxime.[60]

$$(Co^{I}) + XCH{=}CH_2 \xrightarrow{\text{fast}} \underset{CH_2}{\overset{CHX}{\|}}\!\!-\!\!(Co^{I}) \xrightarrow{\text{slow}} XCH_2CH_2(Co^{III})$$

(X = CN, COOR)

Similar addition reactions have also been demonstrated with alkynes.[53,54,61] The mechanism involves nucleophilic attack by (Co^{I}) (syn-addition on the β carbon atom of alkyne, via a π complex, followed by rapid trans addition of a solvent proton:



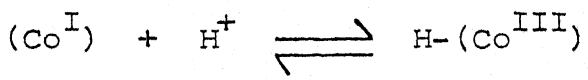
(X = Ph, CO_2R, CH_2OH, CF_3, CH_2CO_2Me)

However, with propargyl alcohol ($X = CH_2OH$) a mixture of α and β substituted products is obtained while propylene ($X = CH_3$) gives only the α-substituted product.

Recently, 2-aryl-2-hydroxyethyl, 2-alkoxyethyl, 2-hydroxyethyl, cobaloximes have also been prepared using this method.[62-64] Synthesis of other novel cobaloximes have been achieved using the similar method.[65]

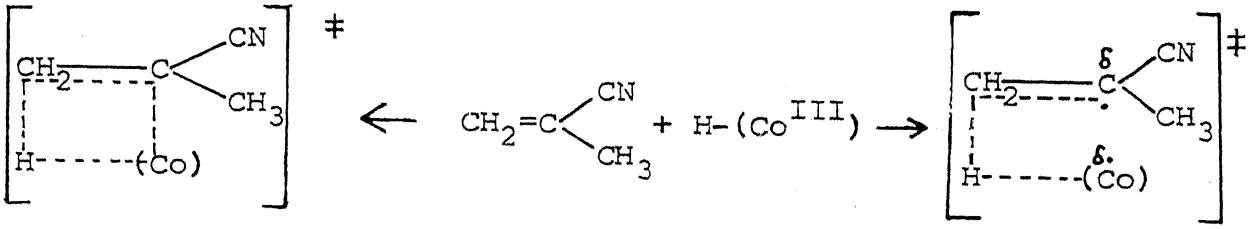
A.2 From cobalt hydride reagent

The (Co^{I}) complexes in less basic medium may reversibly pick-up a proton to give the corresponding cobalt(III) complex with a coordinated hydride:[66,67]



Being the conjugate acid of (Co^{I}) the hydrido complex decomposes

in alkaline medium to (Co^{I}) thereby undergoing most of substitution reactions described for the latter[68] (Sec. 1.3.1/A.1). This reagent, however, has been exploited most for the synthesis of pentacyanocobalt(III) and cobalamin derivatives. Interestingly the addition of hydrido species across the double and triple bond produces α-substituted derivatives, unlike that of (Co^{I}) as discussed previously. Kinetic studies indicate the possibility of two different mechanisms, one with a four centred transition state (12) and the other with a biradical transition state (13), the former being a more favourable one:[60,69]



12 13

Stereochemical course have been investigated by Gaudemer et al.[60,70] The following example provides another interesting variation of the addition reaction of cobalt hydride.[71] The mechanism may involve the attack of the hydrido species on the carbinolamine formed *in situ* from aniline and formaldehyde:

$$H(Co^{III}) + PhNH_2 + HCHO \longrightarrow Ph\text{-}NHCH_2(Co^{III}) + H_2O$$

Monothiocarbamic S-esters have apparently not been described as

ligands, however, by reacting pyridinebis(dimethylglyoximato)-cobalt(II) under H_2 atmosphere with monothiocarbamic vinyl ester, yields corresponding organocobaloxime.[72]

$$Co^{II}(dmgH)_2Py + R_1R_2NC(O)S\text{-}CH{=}CH_2 + 1/2\ H_2 \xrightarrow[25^oC]{MeOH} R_1R_2NC(O)S\text{-}\underset{\displaystyle Co(dmgH)_2Py}{\underset{|}{CH}}\text{-}CH_3$$

($R_1 = R_2$ = n-Pr; R_1 = Et, R_2 = n-Bu;
R_1= Et, R_2 = cyclohexyl)

B. Preparation from cobalt(II) complexes

Cobalt(II) complexes[73a] react with a number of organic and organometallic free radicals to form organocobalt(III) complexes. Alkylation of Co(II) complexes like B_{12r}[73b] and several B_{12} model compounds[67,74-77] by RX show second order kinetics with reaction rate versus $K[Co^{II}][RX]$. The reactivity of RX increases with increasing stability of the radical $R^{\cdot}$ (e.g., along the sequence $CH_2ClCOOR < CHCl_2COOR < CCl_3COOR$ and along the sequence R-Cl < R-Br < R-I. Halpern et al. have proved that these alkylation proceed by the following radical mechanism:[73,78,79]

$$[Co^{II}] + R\text{-}X \xrightarrow{slow} [Co^{III}\text{-}X] + R^{\cdot}$$

$$[Co^{II}] + \dot{R} \xrightarrow{fast} [Co^{III}\text{-}R]$$

Another interesting case is the reaction of tertiary alkylhydroperoxide ($RCMe_2OOH$) (R = Et, Ph etc.) with a number of (Co^{II}) chelates to form $R(Co^{III})$ complexes by the following mechanism:[80]

$$RCMe_2OOH + Co^{II} \xrightarrow{slow} RCMe_2O^{\cdot} + OH(Co^{III})$$

$$RCMe_2O^{\cdot} \xrightarrow{fast} R^{\cdot} + Me_2CO$$

$$\dot{R} + (Co^{II}) \longrightarrow R(Co^{III})$$

The synthesis of organocobalt(III) complexes from (Co^{II}) substrates has proved to be very useful in cases where

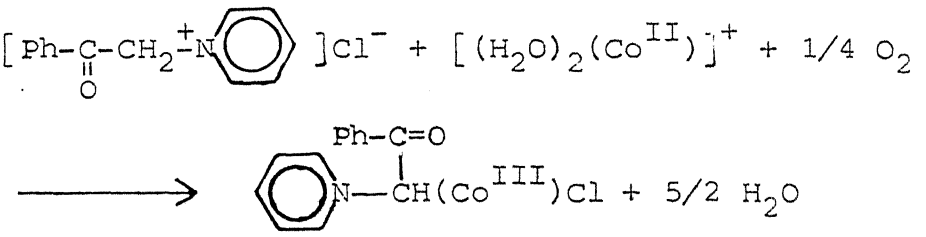
i) the generation of (Co^{I}) is difficult; for example, $[CoMe_6[14]\text{-ane } N_4]^+$, and

ii) the alkylating agent either is very susceptible to decomposition under reaction conditions or react very slowly with (Co^{I}) giving rise to poor yields or no yield of $R(Co^{III})$ at all, for example, many alkylcobaloximes have been synthesized by the reaction of (Co^{II}) with reactive halides such as α-halogeno esters in the presence of zinc wool in non-aqueous solvent.[81]

Organic hydrazines have been shown to react with (Co^{II}) in the presence of molecular oxygen to form corresponding organocobalt(III) complexes:[82]

$$(Co^{II}) + RNHNH_2 \xrightarrow{O_2} R(Co^{III}) + N_2 \quad (R = H, Me, Ph)$$

An interesting example showing the use of (Co^{II}) reagents in the synthesis of (RCo^{III}) derivatives has recently been reported[83]



C. Preparation from cobalt(III) complexes

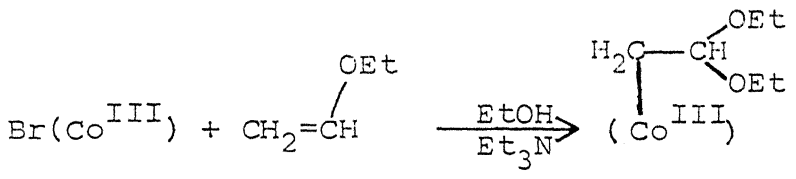
Reaction of (Co^{III}) complexes with nucleophilic carbon species is another method for the synthesis of organocobalt compounds. A number of stable halocobalt(III) complexes react with alkyl and aryl organolithium and organomagnesium reagents to form the corresponding organocobalt(III) complexes.[30,37,84-86]

$$Cl\text{-}(Co^{III}) + PhC{\equiv}CMgCl \xrightarrow{THF} PhC{\equiv}C(Co^{III}) + MgCl_2$$

Poor solubility of halocobalt(III) complexes in ethereal solvents and the use of many-fold excess of Grignard's reagent are two main disadvantages of this method.

Neutral β-methylcobalamin (X = CH_3) is obtained from B_{12a} (X = OH) with a new methylating agent $(CH_3SiF_6)(NHCl)_3$.[87] In another route for the formation of Co-C band, electron rich olefins like vinyl ethers are shown to react with (Co^{III}) complexes like B_{12a} or cobaloximes(III) in alcohols and in the

presence of a base.[88] Evidence for an intermediate olefin-π-complex has been provided:[89]



Because of their sufficient electrophilic character, some hydroxy or alkoxy (Co^{III}) complexes also react with compounds containing an active or enolizable hydrogen.[90-92]

$$RO(Co^{III}) + R^1R^2CH_2 \xrightarrow{EtOH} R^1R^2CH(Co^{III}) + ROH$$

(R = H, Me; R^1 = CN, H; R^2 = CN, $CONH_2$, CO_2Et, NO_2)

Diazoalkanes also react with halocobalt(III) porphyrin complexes to form substituted vinyl cobalt porphyrins.[93]

Analogous compounds of the type $ClCo^{III}(dpgH)_2L$ have also been reported with various L ligands:[94]

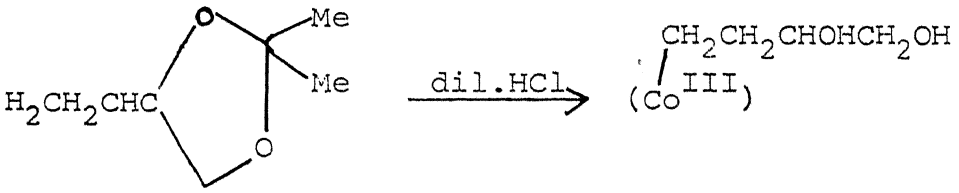
(dpgH) = (diphenylglioxime) and L = Py, α,β or γ-picoline, PPh_3, p-toluidine)

D. Modification of organic ligands

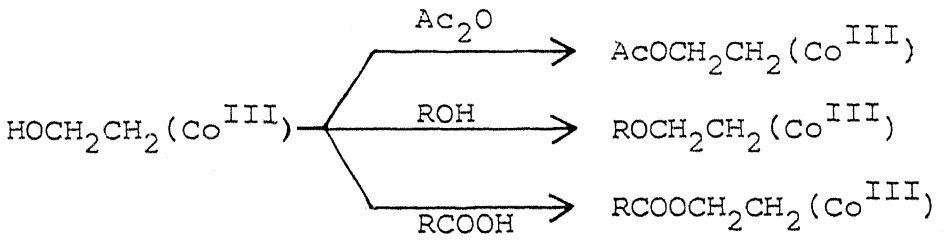
Many organocobalt complexes that are difficult to prepare by the above conventional routes (A, B and C) have recently been synthesized by initially preparing a suitable chelate on which the axial or equatorial group functionalities are then

modified, for example, solvolysis of ester functionality in axial organic ligand provides the simplest route to new cobaloximes.

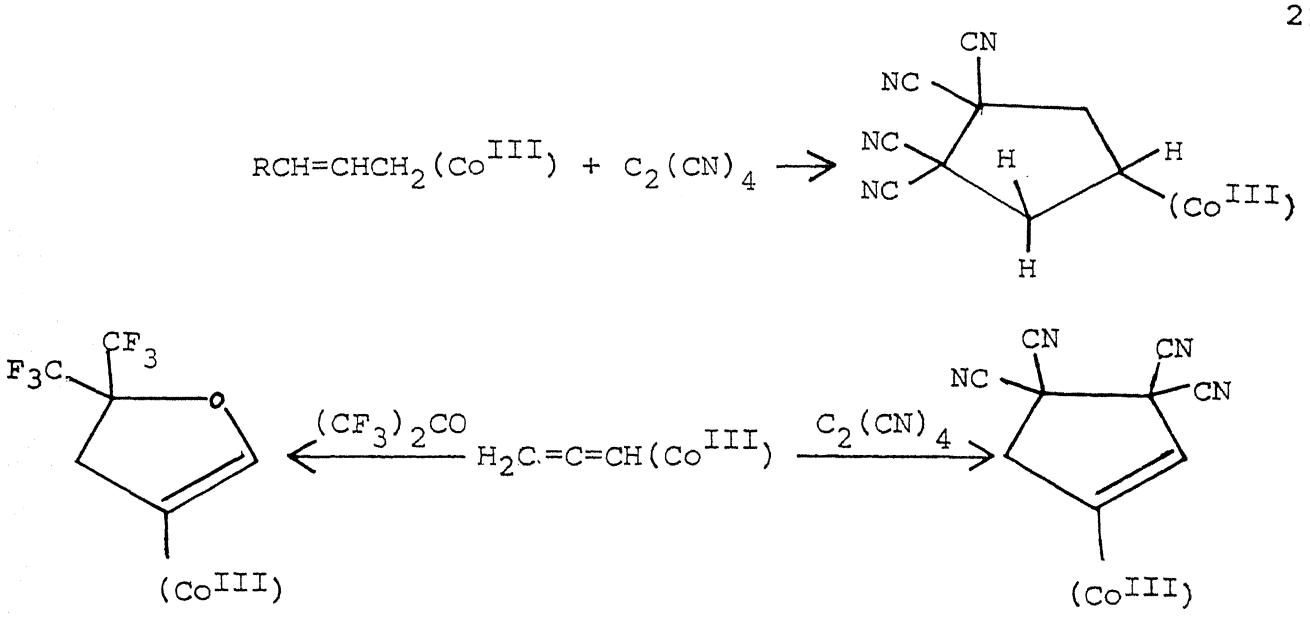
Thus, meta- and para-substituted carboxyphenyl cobaloximes are synthesized in good yields by hydrolysis of corresponding methyl ester in 0.5 M KOH in aq. methanol.[95] Acetal hydrolysis of many cobaloximes and cobalamins also proceed smoothly in acidic medium:[96]



Hydroxy alkylcobaloxime have been used as precursors for many interesting transformation as illustrated below:[97]



Cycloaddition reactions have also been carried out in a number of cobaloximes with tetracyanoethylene and hexafluoroacetone.[98,99]



1.3.2 Novel Organocobaloximes

Among a wide variety of organocobaloximes discussed so far, examples of the following kind of complexes seem very few in literature:

i) cobaloximes with tertiary α-carbon atom,

ii) optically active cobaloximes, and

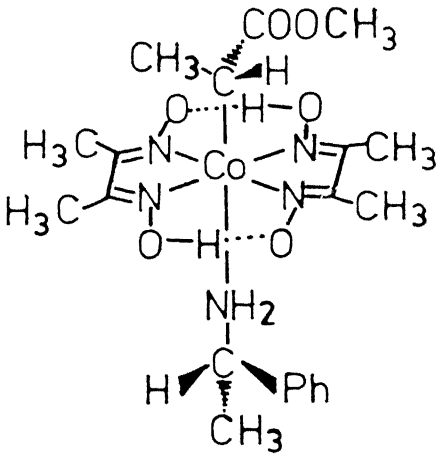
iii) intramolecularly bridged cobaloximes.

Cobaloximes with tertiary carbon bound cobalt are difficult to synthesize probably because of considerable weakening of Co-C bond in such complexes and their susceptibility to eliminate cobalt hydride under reaction conditions. Preparative routes A.1, A.2 and B (Sec. 1.3.1) have been used to synthesize such complexes and the known examples are listed below[100] (Table 1.2).

Table 1.2. The known examples of organocobaloximes with tertiary α-carbon atom

R	Method of Synthesis
Me_2CCN	A.1, A.2
1-Methyl-2,2-diphenyl-cyclopropyl	A.1
t-Adamentyl	A.1
t-Norbornyl	A.2
$MeC(Me)CH=CH_2$	A.1
$MeC(Et)C\equiv CH$	A.1
Me(OAc)(MeCOO)C	A.2
$Cl_2CC(=O)OMe$	B
Cl_2CCN	B
Cl_3C	B
CMe_2COOMe	A

Since organocobaloximes have been used as catalysts in many reactions, a number of optically active cobaloximes have been synthesized with an aim that they will provide precise information about the elementary process of such catalytic reactions.[101-104] Representative examples are illustrated in Fig. 2 (14, 15). Besides, Gaudemer et al. have reported the first example of chiral atropisomeric cobaloxime (Fig. 2) (16)



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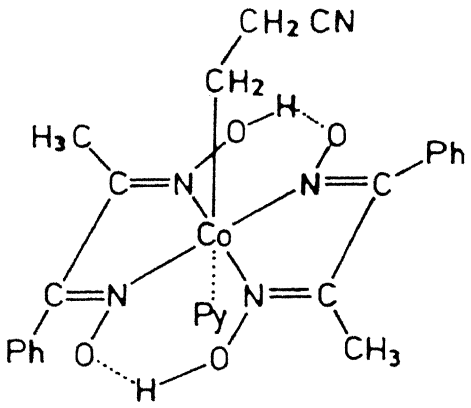
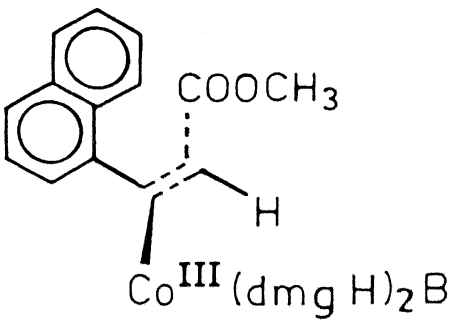
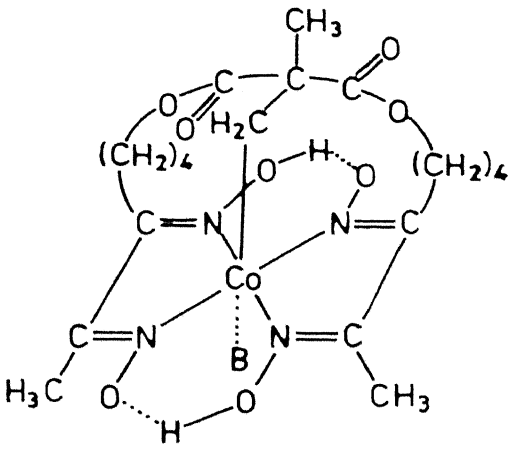


(15)



(16)



(17)

FIG. 2 NOVEL ORGANOCOBALOXIMES.

in which the rotation of the atropisomeric ligand is inhibited by the cobaloxime substituent.[105]

A number of novel intramolecularly bridged cobaloximes (Fig. 2, 17) have also been synthesized to model the B_{12} dependent enzymatic methylmalonyl-Co mutase reaction.[106]

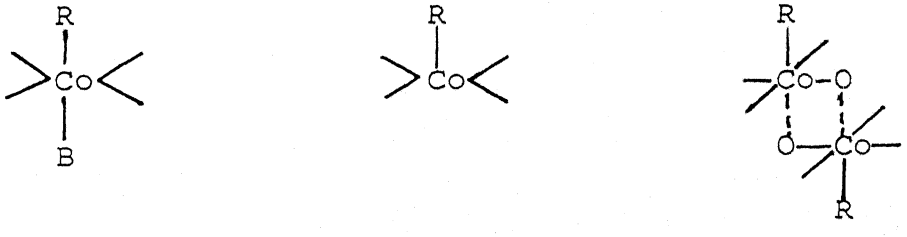
1.4 Cobaloximes: Electronic, Thermodynamic, Electrochemical and Spectral Properties

The structure of organocobalt(III) complexes and the valency of the cobalt ion have been established by a combination of various physicochemical analyses. All organocobalt(III) complexes for which magnetic susceptibilities have been determined are diamagnetic, whether six coordinate, five coordinate or dimeric.[35,107] In general, organocobalt complexes can exist in the three different stereochemical configurations:

a) six coordinate, octahedral, orange in colour,

b) five coordinate, square pyramidal, green in colour, and

c) dimeric, consisting of two square pyramidal complexes, generally red in colour:



[a] octahedral

[b] square pyramidal

[c] bridged octahedral

The four equatorial donor atom groups in all the complexes remain nearly planar but other parts of the chelate ring can exhibit large conformational changes as a consequence of the steric interactions with the axial ligands. Another interesting feature revealed by X-ray studies is the large Co-C-C bond angle observed when the coordinated carbon atom is tetrahedral. It has been suggested that the rehybridization is necessary in order to increase the overlap with the cobalt σ-metal orbital and to reduce repulsions between the non-bonded electron pairs on the cobalt and the electron pairs in the C-C and C-H bonds.[35] Furthermore, there appears to be a linear relationship between the Co-C bond length and the number of substituents on the carbon attached to cobalt. In general, it seems that in the organocobaloximes $[RCo(dmgH)_2B]$, steric interaction between bulky bases B and the equatorial ligand system, bend the equatorial ligand system towards axial organo ligand and provoke lengthening of the Co-C bond even by > 0.1 Å.[108,109]

In the organocobalt(III) complexes of the type $[RCo^{III}(L_4)B]$, the variation of Co-L bond distance is found when the organo group R is replaced by the inorganic ligands such as Cl^-, NO_2^-, or CN^- and this has often been interpreted in terms of the strong trans-influence of the organo group. Indeed, both cis and trans influences have been noted in these complexes. When the equatorial ligand of an organocobaloxime lacks a plane of symmetry, isomers are possible. Similarly, organocobaloximes

where R is optically active are also known.[33,35]

Approximate ab initio studies of geometrical deformation introduced in cobaloximes do not reveal the existence of any major electronic effects.[110] However, theoretical calculations[111,112] indicate that the metal atom of the cobalamin has a slightly smaller partial positive charge than that of cobaloxime, otherwise there is a close similarity in the nature of axial bonds involving the cobalt atom in both[113-115] (Fig. 3).

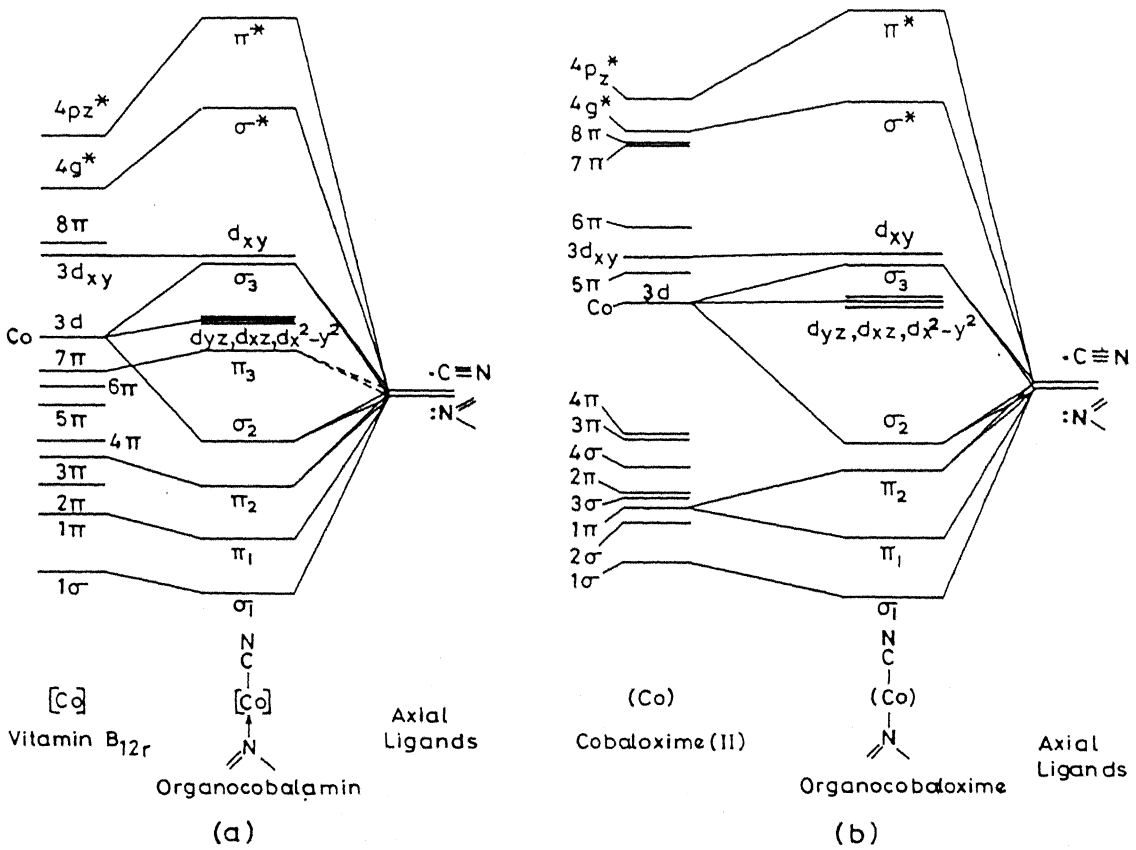


Fig. 3 Schematic M.O. diagram of Cobalamin and Cobaloxime showing the effect of axial ligands[113].

1.4.1 Electronic Spectra

In view of semiempirical calculation and EHMO theory, electronic structure of the cobaloxime has been considered and results of these calculations have been useful in the analysis of the electronic spectra. Three major bands appear for cobaloximes in general:

a) Band at 240 nm, assigned to π-π^* transition (in corrin system), however, this band appears at a higher wave length due to the extensive conjugation.

b) There are several but not well assigned bands between 400-250 nm. The axial bases may absorb in this region.

c) The important low energy absorption of the organocobaloxime occurs between 400-500 nm and is believed to be typical of the presence of covalent axial bonds in view of the ε of about 10^3. This band has been assigned to cobalt to carbon charge transfer band. Its energy depends on the axial base and also to some extent on the inductive effect and the partial 2s character of axial carbon residue attached to the cobalt[116,117] atom. This transition is shifted to higher energy on changing the hybridization of the carbon residue. Considering these arguments, the band can be assigned to σ_2-σ_3,[113] but it has also been assigned to d-π^* transition.[116]

1.4.2 IR Spectra

The vibrational spectra of cobalamins and cobaloximes reflect very broad generalities. Thus, for any alkyl cobaloximes,

the band at 1560 cm^{-1} is attributed to C=N stretching frequency of dimethylglyoximato ligand and is dependent on the strength of the axial base ligand. The bands which may be used for partial characterization are $\nu_{OH\cdots O}$ (1720-1760), ν_{N-O} (1230-1240 and 1080-1100) and ν_{C-N} (dmgH) (510-520) where values in parentheses represent the approximated frequency region[119,120] (in cm^{-1}).

1.4.3 NMR Spectra

Because of diamagnetic nature of these complexes much information about their structure, intramolecular interaction and reactions, has come from the study of ^{1}H NMR,[40,121,122] ^{13}C NMR, ^{19}F NMR and ^{59}Co-NMR spectroscopy.[123-126] ^{1}H NMR spectra of organocobaloximes are generally very simple provided, both the axial ligands are achiral, the four methyl groups on equatorial glyoximato ligand appear as a sharp 12 H singlet around 2.00-2.40δ . This, therefore, has been extensively used in monitoring the reactions of cobaloximes. Besides, ^{1}H NMR has also been used in mechanistic details and structural elucidation in solution phase.[105,127]

1.4.4 Electrochemistry

There are two important reasons why organocobalt complexes have been adopted by nature -

a) variability of coordination number, and

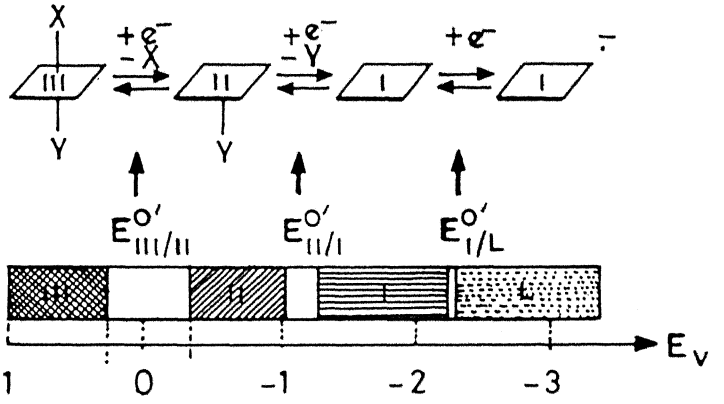
b) variability of oxidation state.

In vitamin B_{12} and related (Co^{III}) complexes generally, (i) (Co^{III}) is ligated by two axial ligands (R, B); (ii) (Co^{II}) by one (B); and (iii) (Co^{I}) by one or none.[128,129]

According to Scheme 1.3, this trend of decreasing coordination number has been qualitatively described by R-Co-B three centred, 4 → 5 → 6 electron, bonding metal orbital having substantial d_{z^2} character.[130,131]

Scheme 1.3

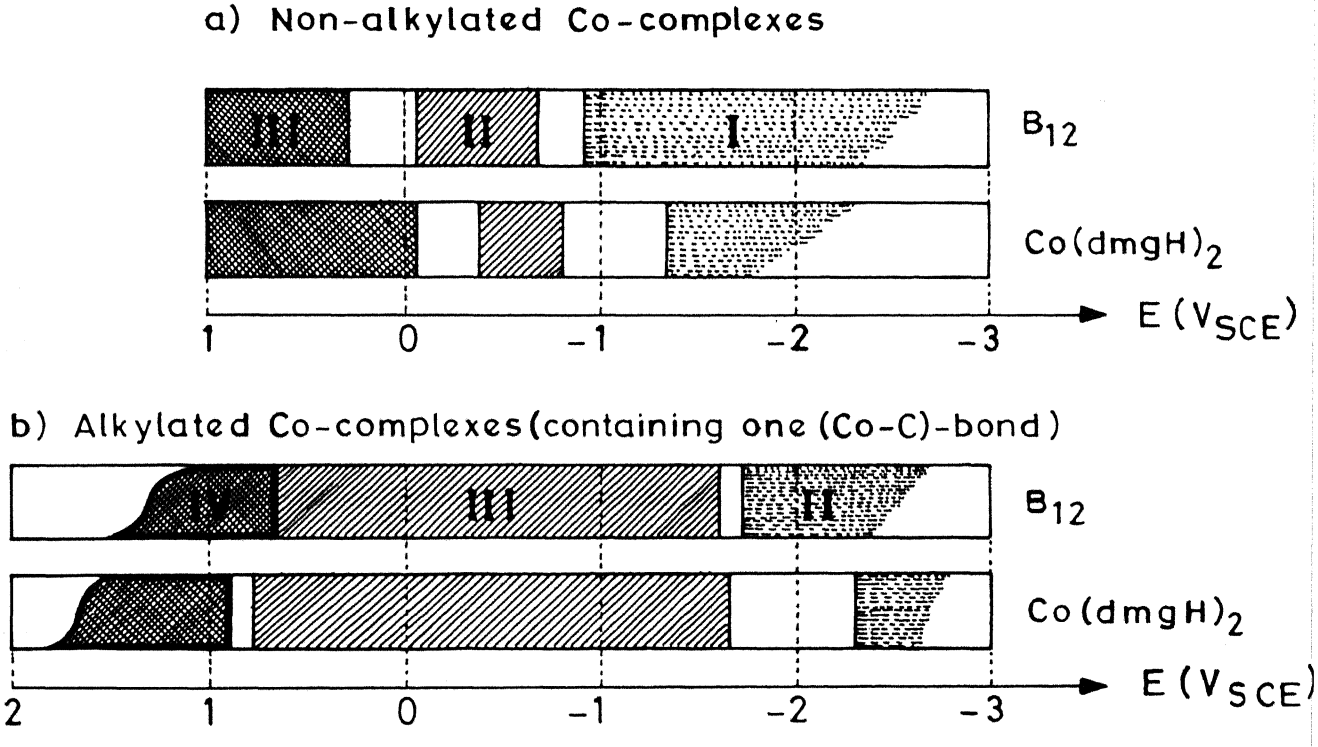
Reduction potentials and related stability-zone



Since metal reduction from +3 → +2 → +1 is coupled with axial ligand expulsion, $E^{\circ}_{3+/2+}$ and $E^{\circ}_{2+/1+}$ depend on the complex formation constant of axial ligands with cobalt in different oxidation states. The thermodynamic stability of different cobalt chelates at variable electrode potential, therefore, can be tabulated. Scheme 1.4 shows the general behaviour of cobaloximes and B_{12} derivatives.

Scheme 1.4

Ranges of Thermodynamic Stability of B_{12} and Cobaloximes at Variable Electrode Potential



In this Scheme (1.4), the E° values are represented by white zone, their width being due to the variation in E° caused by different axial ligands and substituents. The white zones separate stability zones of different oxidation (dark ones) states, as a function of electrode potential. Reported E° values for different axial bases and various solvents/electrolytes (all adopted to S.C.E. reference system) lie within the white zones.

1.4.4.A Electrochemical Reduction

The electrochemical reduction of cobaloximes have received little attention compared to Schiff's base B_{12} models and data available for organocobaloximes are somewhat contradictory. Costa et al. have demonstrated with non-organocobaloximes that i) axial ligand has a marked effect on the $Co^{3+/2+}$ reduction potential, and ii) the nature of the equatorial ligand governs $Co^{2+/1+}$ reduction.[132-134]

Finke, Elliot and coworkers have observed that for alkyl and non-alkylcobaloximes, reduction is irreversible under all conditions of added ligand, solvent, temperature, etc., whereas vitamin B_{12} derivatives undergo reversible electrochemical reduction.[135,136] However, Le Hoang et al. found the electrochemical reduction of organocobaloxime to be reversible for most cases in DMSO.[137] Crumbliss and Morgan have obtained a set of data, which show that as the basicity of axial base ligand increases it becomes more difficult to reduce the cobaloximes, either electrochemically or chemically.[108]

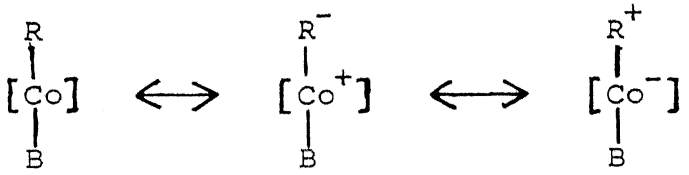
1.4.4.B Electrochemical Oxidations

Organocobaloximes can be oxidised both electrochemically[138-145] and chemically.[138,146,147] EPR data suggests that the oxidised species contains (Co^{IV}).[138,148,149] Halpern et al. have estimated that the unpaired electron resides in a hybrid molecular orbital consisting primarily of 3d character with about 30% contribution from 4p orbital.[148] The oxidised

complexes are unstable at room temperature and undero solvent-assisted dissociation at low scan rates.[142] In the presence of a nucleophile, the decomposition of $R(Co^{IV})$ occurs via nucleophilic attack at the ligating carbon, yielding (Co^{II}) and R-nucleophile, with inversion of configuration.[145] One electron electrochemical oxidation of $RCo^{III}(dmgH)_2.H_2O$ with a variety of R group are found to correlate well with the Taft σ^* parameter for R and with the pK_a of RH. Recently, kinetic and thermodynamic data obtained as a function of R for reversible one electron oxidation of $RCo^{III}(dmgH)_2.H_2O$ in CH_3CN, reflect the importance of steric interaction on oxidation potentials.[143]

1.4.5 Stability of Cobalt-Carbon Bond

Alkyl cobaloximes and alkylcobalamins have been found to be thermally stable organocobalt complexes. Alkylcobaloximes, for example, decompose only at 200°C, pointing towards a stable Co-C bond. One possible way of expressing this axial Co-C bond stability may be through the resonating structure as follows:



A knowledge of Co-C bond character has been derived from the changes in the orbital energies on the formation of the bond between a d^7 (Co^{II}) species and the organic radical. The d-orbital arrangement of the d^7 Co system has been considered

to be intermediate between that for the d^8 system, in which the d_{xy} orbital is belived to be appreciably higher in energy than the d_z^2, and the d^6 system in which the d_z^2 orbitals is of higher energy than the d_{xy} orbital. As the bond formation involves the pairing of the d_z^2 orbital with the carbon sp^3 orbital, the stability of the bond will depend upon the relative energies of these two orbitals and upon the relative energies of the d_{xy} and d_z^2 orbitals. LCAO-MO calculations further indicate that interaction of $3d_z^2$, $4p_z$ and 4s orbital of cobalt with carbon sp^3 orbital is mainly responsible for Co-C bond stabilization. If the organic residue (R) is an sp^2 or sp hybridized carbon, then, additional interactions of the π-carbon orbital with $3d_{xz}$ and $3d_{yz}$ orbitals of cobalt lead to further stabilization of the axial bond. Besides, any changes in the second axial ligand (B = usually base ligand) profoundly affects the stability of the Co-C bond trans to it (trans influence). Thus, more basic ligands have been shown to stabilize the organocobalt(III) complexes further. Like the axial ligand, the equatorial ligand also affects (cis-influence) the Co-C bond stability. This cis-influence, however, is much less pronounced than the trans-influence. Besides the electronic effects, the steric factors also play a marked role in the Co-C bond stability which has been established by X-ray crystallographic analysis. An interesting linear relationship between the Co-C bond length and the number of substituents on the α-carbon to the

metal has been observed.* The Co-C bond dissociation energy of a number of organocobalt complexes and coenzyme B_{12} has recently been estimated by Halpern et al.[144] It ranges from 17-25 kcal mol^{-1}, while in coenzyme B_{12} it is estimated to be 26 kcal mol^{-1}. One can summarize that in all the organocobalt compounds synthesized so far or compounds present naturally, a delicate balance of electronic and steric factors and flexibility of oxidation states of the metal is the strength behind the stability of Co-C bond.

1.5 Reactions of Organocobalt Compounds

Organocobaloximes and related organocobalt complexes undergo four basic types of reaction:[33,36,40,68,151-155]

A. Cobalt-carbon bond cleavage

B. Insertion reactions

C. Reaction of a coordinated ligand

D. Ligand replacement reaction.

1.5.A. Cleavage of the Cobalt-Carbon Bond

Co-C bond cleavage of organocobaloximes may be induced by,

i) reduction or oxidation of organocobaloximes,

ii) electrophilic, nucleophilic or radical attack at

---

* It has been suggested that weakening is triggered by a steric perturbation involving conformational distortion of the corrin ring towards 5'-deoxyadenosyl group.[150]

the group R,

iii) modification within the group R,

iv) charge transfer interaction of the macrocycle with additional reagents,

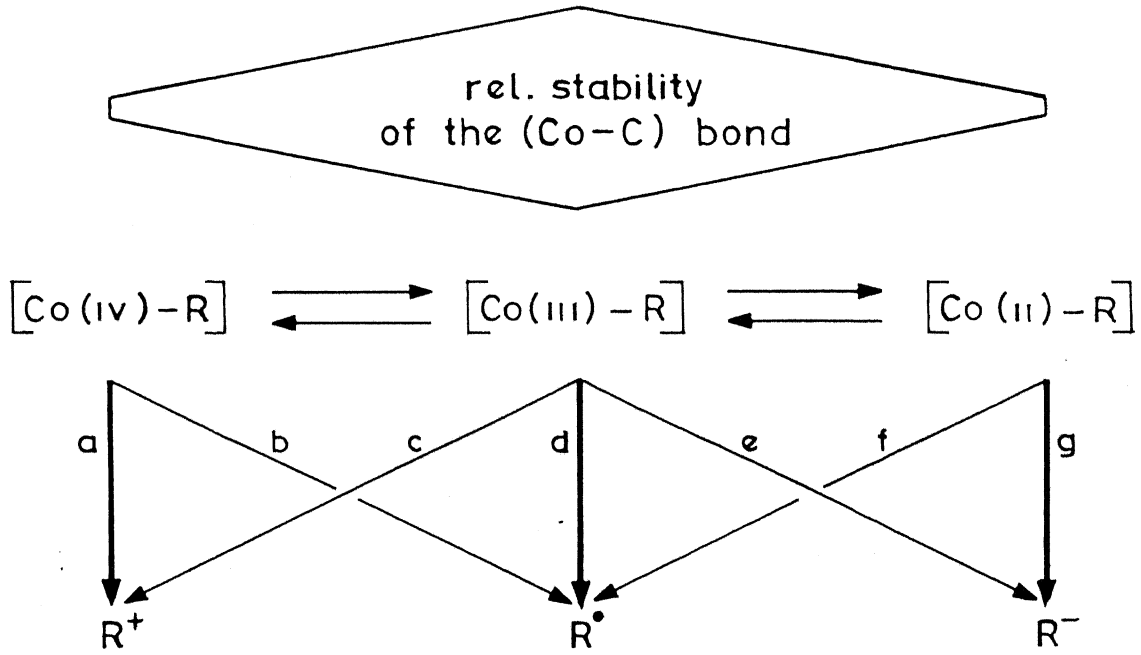
v) axial ligand exchange,

vi) light or heat, and

vii) steric interaction between macrocycle and alkyl group.

An actual cleavage is often caused by combined parameters. Scheme 1.5 depicts the formal routes of Co-C bond cleavage in different oxidation state:[131]

Scheme 1.5



The R group may react as an electrophile in $[R\text{-}Co^{IV}]$ (path a), as radical in $[R\text{-}Co^{III}]$ (path d), or as nucleophile in $[R\text{-}Co^{II}]$ (path g). However, reduction or oxidation of [R-Co] may allow

decay routes b, c, e and f.

Organocobalt complexes on the oxidation level (Co^{II}) or (Co^{IV}) are very unstable, so that first order decay followed by trapping of free organic species by the reagent is favoured.

($R\text{-}Co^{II}$) complexes have been shown to exist. Compared to their parent ($R\text{-}Co^{III}$) compounds they exhibit reduced stability, which depends dramatically on the nature of the macrocycle,[150] the alkyl moiety and the axial base. Radical and anionic decay mechanism (path f or g) have been proposed to explain the recovered reduction products.[156,157] The free radicals formed under reducing conditions may further be reduced to anion, complicating the distinction between path f and g.

One electron oxidized complexes ($R\text{-}Co^{IV}$) exhibit a limited lifetime and can be cleaved by two pathways:

Path a: Nucleophilic attack on ($R\text{-}Co^{IV}$). This occurs with inversion of configuration at the cobalt bound carbon (2nd order rate constants). Intramolecular nucleophilic displacement involving the macrocycle has also been observed on the basis of kinetic results.[141,158]

Path b: Direct homolytic displacement of (Co^{III}) in ($R\text{-}Co^{IV}$).[159]

Organocobalt(III) complexes are usually stable enough to be isolated. The cleavage of Co-C bond in organocobalt(III) complexes is a consequence of an attack by a reagent in a

bimolecular reaction. Redox reactions between oxidizing or reducing reagents and $[R\text{-}Co^{III}]$ may compete with bimolecular substitution reaction. In general, the cleavage can be either heterolytic or homolytic and is broadly encompassed into the following three categories:

<u>Path c</u>: i) $R\text{-}Co^{III} + X^- \longrightarrow RX + (Co^I)^-$

ii) $(^*Co^I) + R\text{-}Co^{III} \longrightarrow {}^*Co^{III}\text{-}R + (Co^I)^-$

<u>Path d</u>: i) $R\text{-}Co^{III} + X^\cdot \longrightarrow RX + (Co^{II})$

ii) $R\text{-}Co^{III} + (^*Co^{II}) \longrightarrow {}^*Co^{III}\text{-}R + (Co^{II})$

<u>Path e</u>: i) $R\text{-}Co^{III} + X^+ \longrightarrow RX + (Co^{III})^+$

ii) $R\text{-}Co^{III} + (^*Co^{III}) \longrightarrow {}^*Co^{III}\text{-}R + (Co^{III})^+$

<u>Path c</u>: Cleavage by nucleophiles

A few nucleophilic displacement reactions at cobalt have been studied. Representative examples are shown in Scheme 1.6.

In principle, for such reactions the nucleophile X^- must have a strong affinity towards the α-carbon bound to cobalt. The possible reversibility depends upon the ability of (Co^I) species as a leaving group, the incoming nucleophile as

Scheme 1.6

Nucleophilic Displacement at Cobalt-Carbon Bond

$$CH_3(Co^{III}) + X^- \longrightarrow CH_3X + (Co^I)^-$$

(X^- = Cl^-, Br^-, I^-, CN^-, RS^-, $NRPh^-$ etc.)

$$cis\text{-}PhCH{=}CH(Co^{III}) + CH_3Li \longrightarrow cis\text{-}PhCH{=}CHMe + Li^+(Co^I)^-$$

$$H_2C{=}C{=}CH(Co^{III}) + BH_4^- \longrightarrow H_2C{=}C{=}CH_2 + (Co^I)^-$$

$$OH(Me)CHCH_2(Co^{III}) + OH^- \longrightarrow Me_2CO + (Co^I)^- + H_2O$$

$$H_3C\text{-}C(=O)(Co^{III}) + NH_2OH \longrightarrow CH_3CONHOH + (Co^I)$$

$$CH_3(Co^{III}) + \left(Co^I(chgH)_2Py\right)^- \rightleftharpoons CH_3Co^{III}(chgH)_2Py + (Co^I)^-$$

[Co = $Co(dmgH)_2Py$; chgH = cyclohexylglyoxime monoanion]

well as their carbon basicities. When the reactions are carried out under aerobic conditions, oxygen removes (Co^I) from solution and reaction becomes faster. In contrast, no reaction should occur in the absence of oxygen. Since reactions in both aerobic and anaerobic conditions are reported, ambiguity, therefore, prevails about this class of reactions. Nucleophilic metal to metal exchange reactions, however, have been conclusively proved to be of S_N2 type with inversion taking place at the cobalt bound to α carbon of the substrate complex.[160] The base catalysed decomposition of β-substituted

ethyl-cobalt(III) complexes either proceed via concerted mechanism or by an intermediate π-complex formation.[63,67,161] Recently, nucleophilic acylation of Michael olefins have been reported using vitamin B_{12} as catalyst. The action of the catalyst involves the formation and cleavage of Co-C bond using (Co^{I}) as a reactive intermediate acting in a nucleophilic[162] manner.

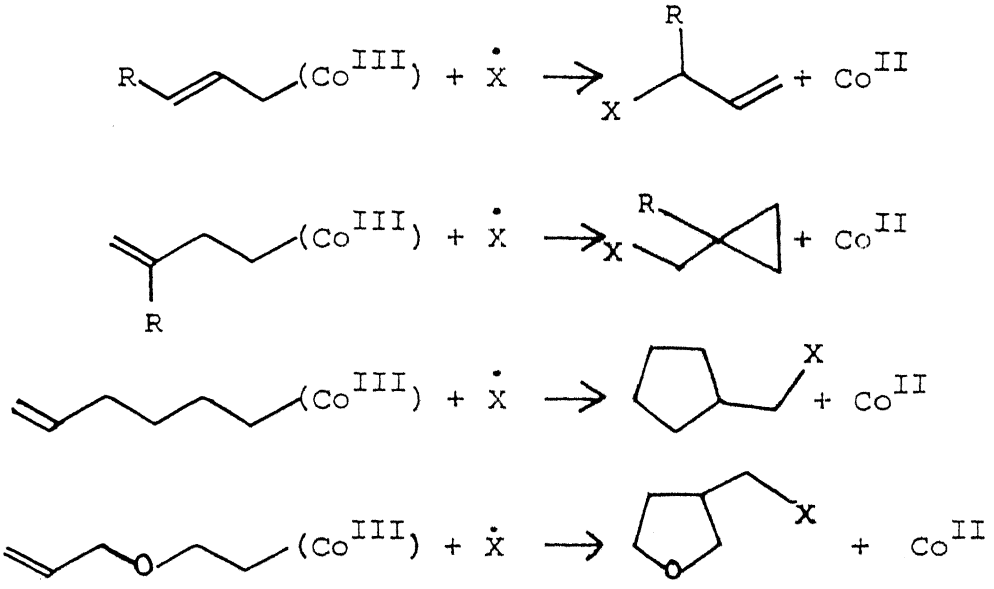
Path d: Homolytic cleavage of cobalt-carbon bond

Homolytic displacement of a radical $\dot{Y}$ from a carbon centre by another radical $\dot{X}$, the S_H2 reaction, is of immense importance in synthetic organic chemistry.

$$\dot{X} + RCH_2Y \longrightarrow RCH_2X + \dot{Y}$$

However, these reactions are rarely[153,163] observed not because they are theoretically impossible, but because other processes take precedence. Although homolytic displacement reactions are observed for boron, tin and lead, authenticated examples for saturated sp^3 hybridized carbon are still rare. Organocobaloximes because of their low Co-C bond energy (17-25 kcal mol^{-1}) have been found to be the best suited for such reaction. d^7 low spin cobaloxime(II) has been shown to be a good, stable leaving group in many regiospecific substitution reactions of C, S or N centred electrophilic free radical precursors with a variety of organocobaloximes. Some examples of homolytic substitution

in organometallic complexes are illustrated below:[164-191]



$R_2C{=}C{=}CH\text{-}Co^{III} + \dot{X} \longrightarrow XCR_2C{\equiv}CH + Co^{II}$

$Ph\text{-}C{\equiv}C\text{-}CH_2\text{-}Co^{III} + \dot{X} \longrightarrow XC(Ph){=}C{=}CH_2 + Co^{II}$

($X = CCl_3$, CCl_2CN, CBr_3, SPh, RSO_2, $ArSO_2NMe$ etc.; $Co^{III} = Co^{III}(dmgH)_2Py$).

These reactions because of their novelty and synthetic potential have generated a lot of interest among chemists in recent past. The key step in the above reactions involves the homolytic displacement of a low valent metal complex by attack of a carbon, nitrogen or sulphur centered radical at unsaturated or saturated carbon of the organic ligand of the organometallic complex. The overall reaction sequence is outlined below:

Initiation : $RML_n \rightleftharpoons \dot{R} + \dot{M}L_n$

Propagation : $\dot{M}L_n + XY \longrightarrow XML_n + \dot{Y}$

$\dot{Y} + RML_n \longrightarrow RY + \dot{M}L_n$

Termination : $\dot{Y} + \dot{M}L_n \longrightarrow YML_n$

$\dot{Y} + \dot{Y} \longrightarrow Y_2$

In general, the attack of $\dot{Y}$ takes place at the terminal carbon of the unsaturated organic group like allyl, allenyl, hexenyl etc. However, exception to this is also reported.[153,179]

We have recently shown from our laboratory, the first example of α-attack in allenyl and propargyl cobaloximes.[179] Such an attack is controlled by various factors like the electrophilicity of the attacking radical, the electron densities at the nucleophilic centres (α or γ) in organocobaloximes, reaction conditions etc:

$$R_2C{=}C{=}CH\text{-}Co^{III} + ArSO_2Cl \xrightarrow{h\nu} R_2C{=}C{=}CH\text{-}SO_2Ar + ClCo^{III}$$

(R = H)

$$\downarrow h\nu$$

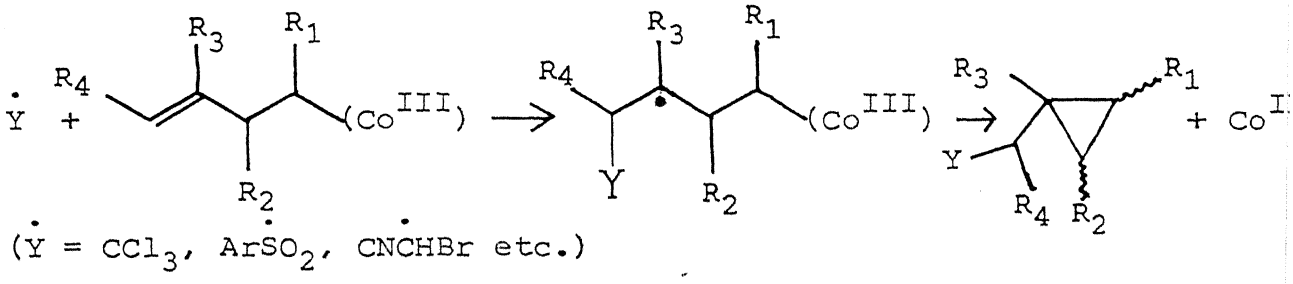
$$CH{\equiv}C\text{-}CR_2SO_2Ar + ClCo^{III}$$

(R = Me)

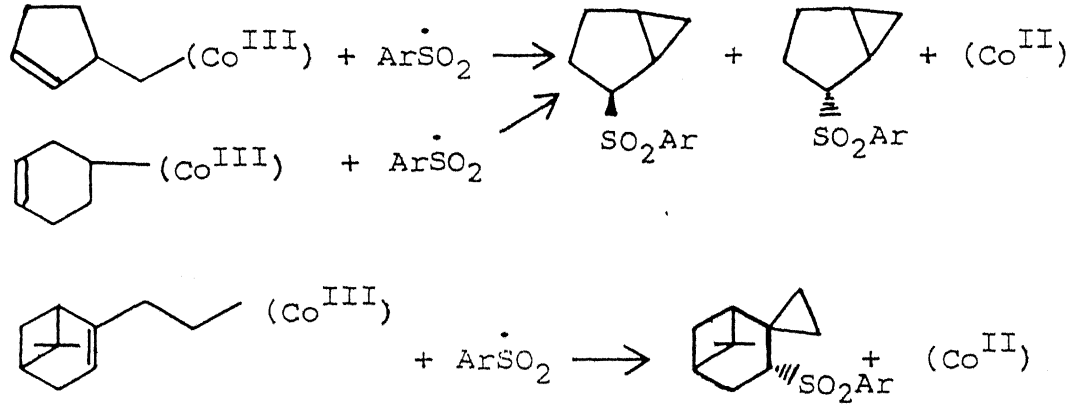
$$CH{\equiv}C\text{-}CH_2\text{-}Co^{III} + ArSO_2Cl \xrightarrow{h\nu} HC{\equiv}C\text{-}CH_2SO_2Ar + ClCo^{III}$$

($Co^{III} = Co^{III}(dmgH)_2Py$)

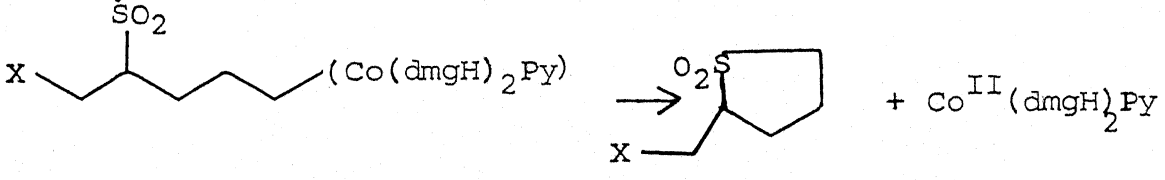
A number of reactions have been described[192] in which the attack of the free radical at the unsaturated carbon centre is followed by the intramolecular homolytic displacement at the saturated α-carbon atom:



Spiro and fused cyclopropane systems have been synthesized[153] by the reaction of appropriate cycloalkenyl cobaloximes with free radical precursors by similar S_H2 reactions:



The formation of sulpholanes by the intramolecular attack of remote sulphonyl radical on the α carbon of the substituted alkyl cobaloximes (S_{Hi}) has been described.[173]



Free radicals, generated by Co-C bond homolysis (by photochemical methods) have recently been trapped with many useful functional groups.[185]

Interestingly, Espenson et al.[193,194] and others[195,196] have criticised that the products and other features in the reactions described above only suggest but do not prove the concept of homolytic displacement by such free radicals. They have proposed that the radical addition takes places at the nitrogen end of N=C bond of the macrocycle cis to Co-C bond, followed by reductive elimination. Scattered examples of the study by captodative radicals with organocobaloximes are also noted in literature.[197]

Path e: Cleavage by electrophile

A variety of electrophilic reagents viz., protonic acids, metal ions, halogen molecules etc. induce Co-C bond cleavage as illustrated in Scheme 1.7.

The mechanism of the acid catalysed decomposition of β-hydroxy alkyl (Co^{III}) complexes have been studied[198-200] in detail. Thus, formation of ethylene from $HOCH_2CH_2(Co^{III})$ is believed to proceed via an intermediate π-complex between cobalt and ethylene. On the other hand, $HOCH_2(CH_3)CH(Co^{III})$ undergoes reversible isomerization to $CH_3CH(OH)CH_2(Co^{III})$ prior to alkene release.

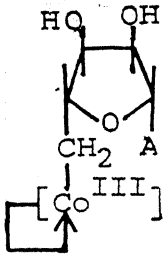
Scheme 1.7

Cleavage of Co-C bond by electrophiles

Acid catalysed cleavage

$$ROCH_2CH_2(Co^{III}) \xrightarrow{H^+} H_2C{=}CH_2 + ROH + (Co^{III})^+$$

(R = H, Me, Et, etc.)

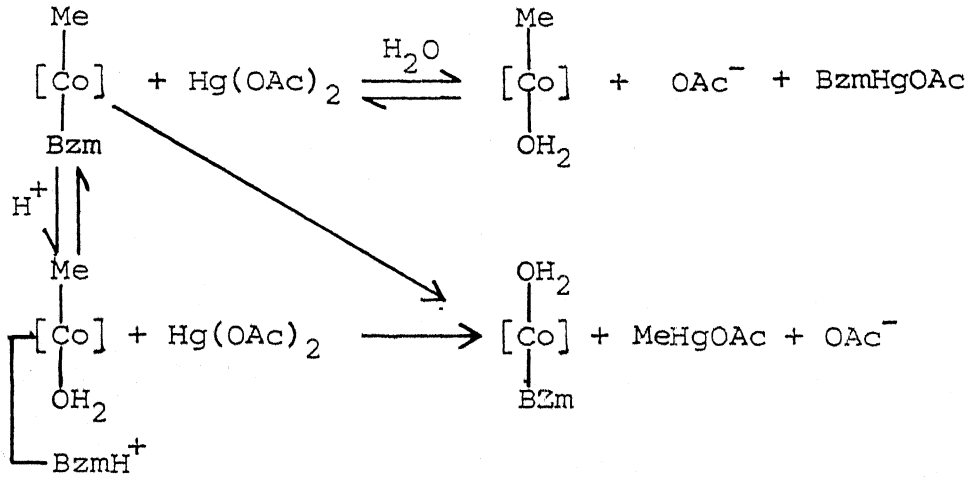


$$\xrightarrow{H^+} B_{12s} + H_2C{=}CHCH(OH)CH(OH)CHO + A$$

(A = adenine)

Cleavage by metal electrophiles

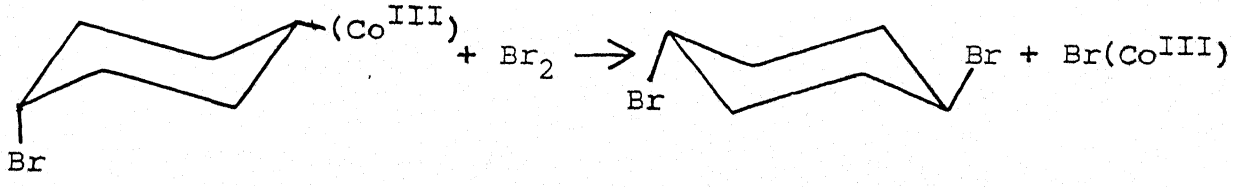
$$cis\text{-}PhCH{=}CH(Co^{III}) + Hg(OAc)_2 \longrightarrow cis\text{-}PhCH{=}CH(HgOAc) + AcO(Co^{III})$$



Halogenation

$$[(S)\text{-}(+)C_6H_{13}CHMe(Co^{III})] + Br_2 \longrightarrow (R)\text{-}(-)C_6H_{13}CHMeBr + Br(Co^{III})$$

$$+ C_6H_{13}CHBrCH_2Br + C_5H_{11}CHBr\,CHMeBr$$



Metal ions have been reported to replace the alkyl group of alkylcobaloxime and cobalamins by S_E2 mechanism. Mercury(II) reagents are particularly effective in cleaving the Co-C bond by attack at the α carbon. Methyl cobalamin by S_E2 mechanism gives rise to methyl mercury(II) ion, $MeHg^+$. The formation of toxic $MeHg^+$ can take place in aqueous environment and the dire consequences caused by the presence of $MeHg^+$ and Hg^{2+} in an ecological system are illustrated by events which occurred in Minamata, Japan.[151] The interaction of methyl cobalamin with mercury(II) acetate in water involves two steps as depicted in Scheme 1.7.

Chromium(II) effects a reductive cleavage of Co-C bond of organocobalamin, the mechanism being either S_H2 (direct displacement) or redox S_E2 involving carbanion transfer to chromium(III).[151]

Halogenation studies have been carried out on a number of organocobalt(III) complexes.[33,36] The halogenation of alkyl cobalt(III) complexes originally interpreted as electrophilic substitution[201] has recently been shown to proceed via an oxidation followed by nucleophilic attack[145] or oxidation followed by radical attack[159] or by an electron transfer mechanism.[202] Many kinetic[203,204] and sterochemical[54,201,205-208] studies have also been reported. In the reaction of iodine with alkyl cobaloximes, a two step process, involving a pre-equilibrium followed by a bimolecular rate determining step in which

the intermediate $R(Co^{III})H_2O.I_2$ acts as an electrophile, has been pointed out:[204]

$$R(Co^{III})H_2O + I_2 \rightleftharpoons R(Co^{III})(H_2O)I_2$$

$$R(Co^{III})(OH_2).\ I_2 + R(Co^{III})H_2O + I_2 \rightarrow 2\ RI + 2[I(Co^{III})H_2O]$$

A base-off process followed by a rapid inner sphere electron-transfer has also been reported for the cleavage of Co-C bond.[209]

1.5.B Insertion Reactions

Studies on the photochemical and thermal insertion of molecular oxygen, sulphur dioxide and sulphur into Co-C bond in many alkyl, allyl, vinyl, allenyl, aryl and benzylcobaloximes have been carried out.[33,35,36] The reaction conditions vary from irradiation of a solution of organocobaloxime at low temperature (ca. $-40^{\circ}C$) to heating at 40-$60^{\circ}C$. Sulphur dioxide insertions with liquid SO_2 in sealed tube under irradiation have also been carried out. The yield of the product is nearly quantitative in most of the cases.

In view of kinetic,[210,211] ESR[212,213] and stereochemical studies[214,215] the participation of free radicals has been confirmed in such reactions and the following two alternative mechanisms have been proposed:

Mechanism 1:

$$R(Co^{III}) \underset{\leftarrow}{\overset{h\nu/\Delta}{\rightleftharpoons}} (Co^{II}) + \dot{R} \xrightarrow{X} (Co^{II}) + \dot{R}X \longrightarrow RX(Co^{III})$$

Mechanism 2:

$$R(Co^{III}) \rightleftharpoons R^{\cdot} + (Co^{II})$$

$$(Co^{II}) + X \longrightarrow X(Co^{II})$$

$$X(Co^{II}) + R(Co^{III}) \longrightarrow RX(Co^{III}) + (Co^{II})$$

$$(Co^{II}) + X(Co^{II}) \longrightarrow (Co^{III})X(Co^{III})$$

($X = O_2$, SO_2)

However, in few cases the insertion reaction has led to the formation of organic or inorganic byproducts along with the expected compound.[170,216]

$$PhCH(Me)(Co^{III}) \xrightarrow[O_2,\ 30^{\circ}C]{CH_2Cl_2} Ph(Me)CHOO(Co^{III}) + Cl_2CH(Co^{III}) + ClCH_2(Co^{III}) + Cl(Co^{III})$$

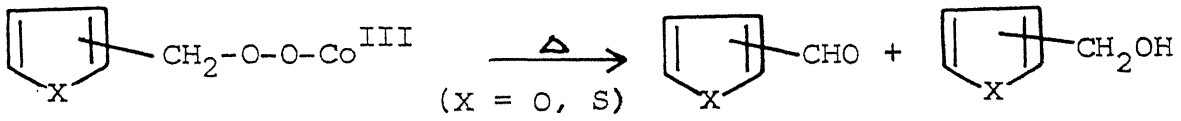
$$Me_2C{=}CHCH_2(Co^{III}) \xrightarrow{SO_2} CH_2{=}CHC(Me)_2SO_2(Co^{III}) + Me_2C{=}CHCH_2SO_2C(Me)_2CH{=}CH_2$$

Decomposition studies of the inserted cobaloximes under various conditions have been carried out, which gives organic products from an initial cleavage of the cobalt-axial ligand bond.[217-219]

$$RR'CHCOO(Co^{III}) \xrightarrow[\text{Methanol}]{NaBH_4} RCHOHR' + OH(Co^{III})$$

$$PhCH{=}CHCH_2SO_2(Co^{III}) \xrightarrow[H_2O]{SO_2} PhCH{=}CHCH_3 + O_3S(Co^{III})$$

$$RS_4(Co^{III}) \xrightarrow{h\nu/\Delta} RS_4R + (Co^{III})S_4(Co^{III})$$



Although oxygen and sulphur dioxide insertion reactions have been pursued in great detail, a few other insertion reactions have also been attempted:[35]

$$R(Co^{III}) \xrightarrow[h\nu]{R'OH,\ CO} R\text{-}O\text{-}\overset{\overset{O}{\|}}{C}\text{-}(Co^{III})$$

$[(Co^{III}) = Co(salen)H_2O,\ Co(acacen)H_2O]$

A case of photochemical substitution reaction of alkylcobaloximes by hydroperoxides leading to dioxy products has been reported.[195]

$$R(Co^{III}) + 2\ R'\text{-}OOH \xrightarrow[C_6H_6/N_2]{h\nu} R'OO(Co^{III}) + ROOR'$$

However, a reinvestigation of the above work with (Co^{II}) and tert-butyl hydroperoxide suggests the participation of $Me_3COO^{\bullet}$ and $Me_3CO^{\bullet}$ radicals in a chain sequence:[220]

$$2\,Me_3COOH + 2(Co^{II}) \longrightarrow HO(Co^{III}) + Me_3COOH(Co^{III}) + Me_3COH$$

Recently, work from our laboratory has led to the observation that the sulphur dioxide insertion into organocobaloxime is not true insertion but occurs by a radical chain process.[221]

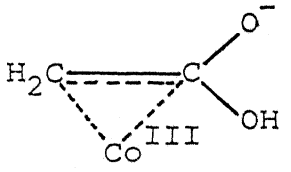
1.5.C Reaction of the Coordinated Ligands

The reactions of coordinated ligands in organocobaloximes include, (i) protonation, deprotonation at axial or equatorial ligand sites, (ii) reactions involving β-carbon of the axial ligand and (iii) σ-π migration at the axial ligand.

Cobaloximes carrying acidic functional groups in its axial organic ligands get converted into corresponding conjugate bases in alkaline medium.[95]

$$HOOCH_2C(Co^{III})H_2O \rightleftharpoons [OOCCH_2(Co^{III})H_2O]^- + H^+$$

The acidities of cobaloximes largely depend upon the inductive and hyperconjugative effect of $[-CH_2(Co^{III})B]$ moiety and also upon the extent of σ-π conjugation as follows:



The electron donating induction effect of cobaloxime moiety is usually very high. Furthermore, the hyperconjugative effect of

the cobaloxime substituent [$-CH_2(Co^{III})X$] in benzyl cobaloximes decreases in the order;[222] ($X = CN^- > NO_2^- > N_3^- \gg Cl^- \gg Br^- > SCN^- > I^-$).

Since many axial base ligands and equatorial ligands have acidic sites, the proton loss can take place from these sites under suitable basic condition, as shown below:[36]

$$R(Co^{III})(OH_2) + OH^- \rightleftharpoons [R(Co^{III})(OH)]^- + H_2O$$

$$PhCH{=}CH(Co^{III}) + CH_3Li \longrightarrow Li^+[PhCH{=}CHCo(dmgH)(dmg)Py]^- + CH_4$$

On the other hand the protonation of the equatorial dimethylglyoximate ligand has been reported:[223]

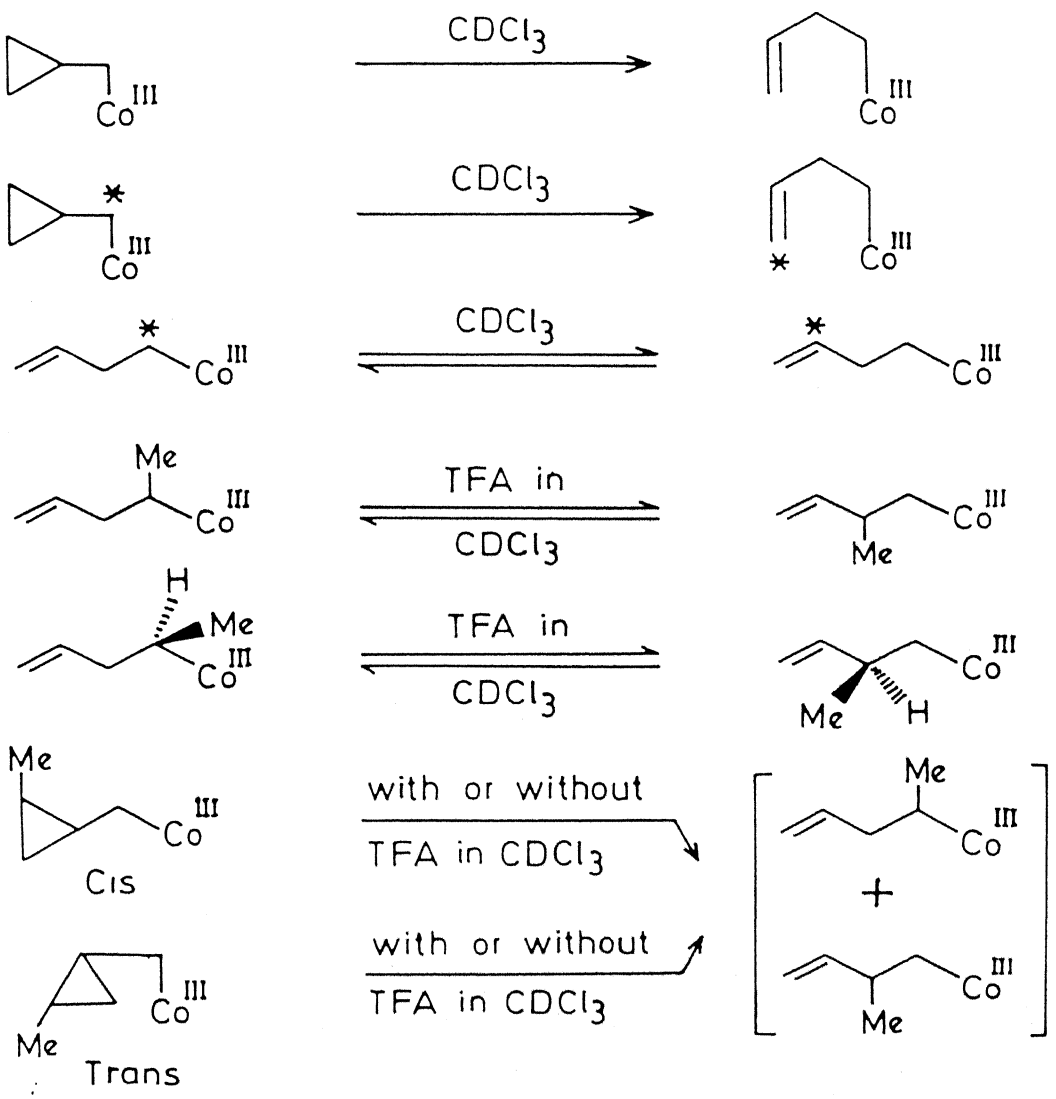
$$R(Co^{III})(OH_2) + aq.HCl \rightleftharpoons [RCo(dmgH)(dmgH_2)Cl] + H_3O^+$$

The β-carbon atom in complexes of the type $AcOCHRCH_2(Co^{III})$ is very reactive and in water or alcohol readily affords the solvolysis product $OHCHRCH_2(Co^{III})$ or $R'ORCHCH_2(Co^{III})$.[96] Many reaction of this type are discussed earlier in Sec. 1.3.1.D.

A number of reactions have been reported by Johnson[224] and Golding,[225] in which the axial organic ligands in cobaloximes undergo σ-π migration to give new cobaloximes as illustrated in Scheme 1.8). These reactions are of considerable

Scheme 1.8

σ - π Migration



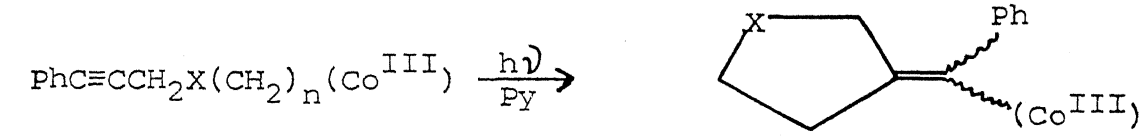
Co^{III} = $Co(dmgH)_2$ Py

TFA = CF_3COOH

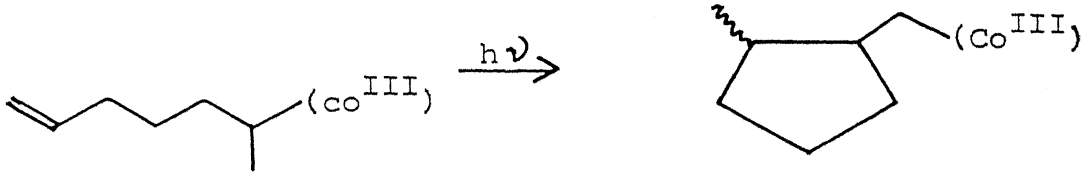
106244

synthetic interest and have played a convincing role in the model studies of B_{12}-dependent diol dehydrase and α-methylglutarate mutase reactions as described in Section 1.3.1.D.

Very recently, Johnson has reported a number of reactions in which substituted alkyl cobaloximes, on photolysis, undergo rearrangement to more stable substituted alkyl- or alkenyl-cobaloximes.[175] The rearrangements have been rationalised in terms of a reversible homolysis of the cobalt-carbon bond, rearrangement of the organic radical and recapture by the (Co^{II}) fragment to give new cobaloximes that are more stable to irradiation than their precursors:



(X = CH_2, n = 1, 2, 3; X = O, n = 2, 3)



1.5.D Ligand Substitution Reactions

The most important class of the ligand substitution reactions in cobaloximes involves direct displacement of an axial base ligand by another base ligand or a cobaloxime moiety as shown in the following examples:[33,175]

$$R(Co^{III})B + B' \longrightarrow R(Co^{III})B' + B$$

(B = H_2O; B' = Py, imidazole, PPh_3 etc.)

$$R(Co^{III})H_2O + CNX\ (Co^{III})B \longrightarrow R(Co^{III})CNX(Co^{III})B + H_2O$$

(X = S, Se; B = Py, piperidine etc.)

An axial base is often replaced by another ligand having stronger affinity for cobalt.[34] For bases having different donor atoms the affinity decreases in the order P > N > S > O while, for bases with same donor atom, such as pyridine and its derivatives, the affinity order follows that of the basicity of the ligands. It is noteworthy that the substitution of a base ligand is not only dependent upon the incoming ligand but also on the trans-influence of the axial organic ligand over the axial base ligand.[108] This effect tends to labilize the cobalt-base bond and may even result in the formation of a five coordinated species by the elimination of the base. The two effects as discussed above, have been very well demonstrated by kinetic studies. Thus, the first order rate of dissociation of trimethylphosphite from $[R(Co^{III})P(OMe)_3]$ decreases in the order: $R = Me_3SiCH_2- > -CH_2F > -CHF_2 > -CH_2Cl > -CF_3 \approx -CHCl_2 \approx -CH_2Br > -CHBr_2$.[226] On the other hand, the rate of axial base exchange in $[CH_3(Co^{III})B]$ decrease in the order of B = $CH_3CN \approx PhSO \approx Me_2SO > Me_2S > Me_3N > Et_3N > Ph_3P > P(OMe)_3$.[227]

The substitution reactions by $CNX(Co^{III})B$ group have been studied in some detail.[228] The tendency in the formation of the

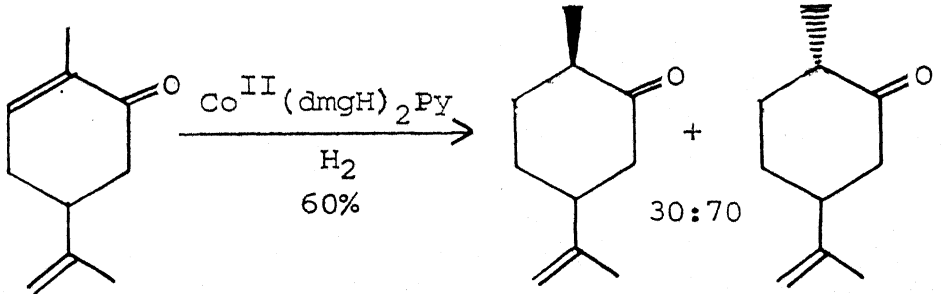
pseudo halide bridged dimer $R(Co^{III})CNX\ (Co^{III})B$ decreases with CNX = NC> NCS> NCSe> SCN>>OCN. However, in the presence of trace amount of cobaloxime(II); oligomers of the type $R(Co^{III})\ \{CNX(Co^{III})\}_n[CNX(Co^{III})B]$ have been formed.

1.6 Organocobaloxime as a Potential Synthetic Precursor

In recent years the physical and chemical studies on organocobaloximes appear to focus on their chemistry as more of an independent area rather than as model for vitamin B_{12} chemistry. Furthermore, with the recent observations that cobaloximes can be used as potential industrial catalysts and synthetic inorganic mediator in carrying out a number of interesting and useful chemical transformations, a new field of research is emerging. Few representative examples of this area are given below.[131]

A) Hydrogenation of olefins

Cobaloximes offer selective, specific and mild conditions for hydrogenation of activated or conjugated olefins (Eqn. 1):



.. (1)

Asymmetric induction during catalytic hydrogenation has been observed in the presence of cobaloxime(II) having optically

active bases (Eq. 1, quinine), for example, α-phenylacrylophenone affords 1-methyl-2-oxo-stilbene in enantiomeric excess of 49%.

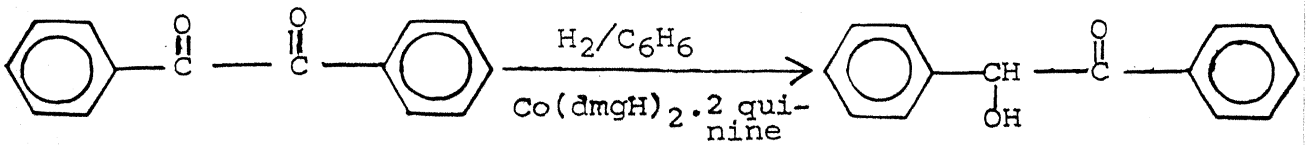
B) Reduction of functional groups

Reduction of several functional groups like C-halo, NO_2, NO, C=NOH, C=N-R, N≡N- by $[Co^{I}(dmgH)_2Py]$ generated *in situ*, has been reported.

$$p\text{-}NO_2C_6H_4CH{=}CH_2CO_2Me \xrightarrow[Co(dmgH)_2.2H_2O]{H_2/1\ hr,\ CH_3OH} p\text{-}NH_2C_6H_4CH_2\text{-}CH(CO_2Me)CH_2 \quad .. (2)$$

$$PhHC{=}NSO_2Ar\text{-}CH_3\text{-}4 \xrightarrow[H_2]{Na[Co(dmgH)_2Py]} PhCHNHAr\text{-}CH_3\text{-}4 \quad .. (3)$$

Asymmetric induction as in Eqn. (1) is also reported (Eqn.4):

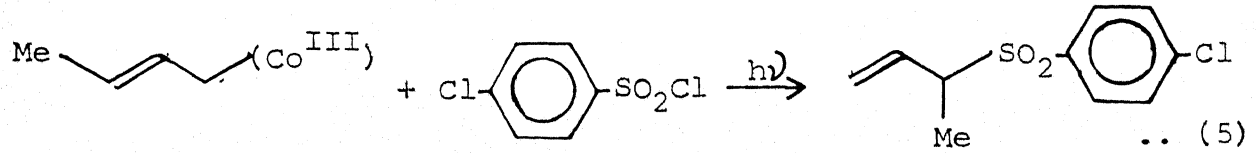


S(+)benzoin (98%)

.. (4)

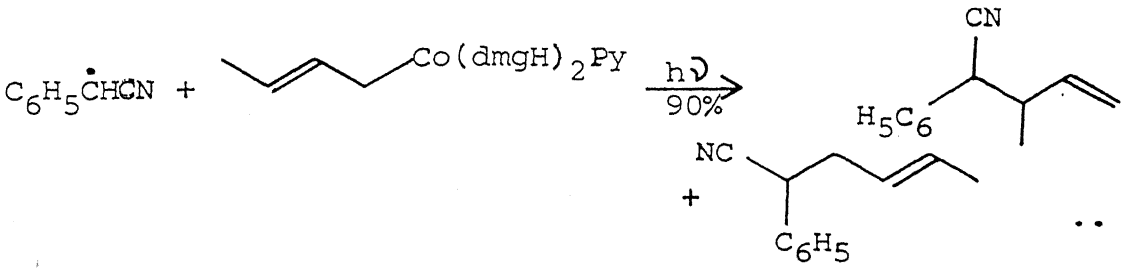
C) Intermolecular formation of aliphatic C-C bond

The homolytic bimolecular displacement of (Co^{II}) from allyl, allenyl, butenyl and benzyl etc. cobaloximes by organic radicals (discussed in Section 1.5.A.d) offers a great potential for the synthesis of several compounds (Eqn. 5):



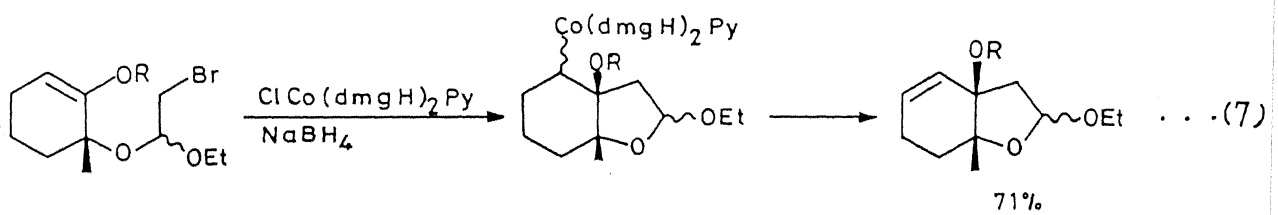
.. (5)

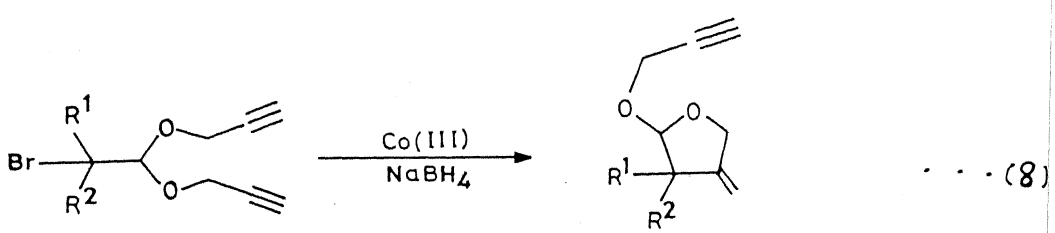
Allylation of nitriles has recently been reported by Gaudemer et al. (Eqn. 6):

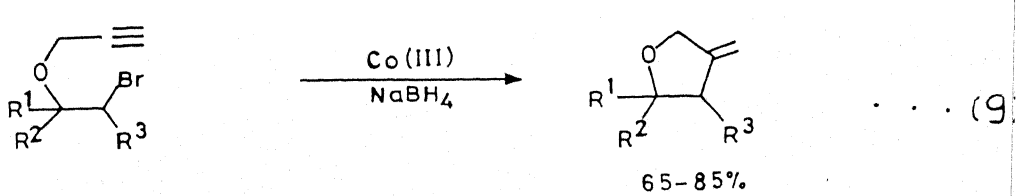


D) Intramolecular formation of aliphatic C-C bond

A number of reactions are recently reported in which an initial electron transfer from (Co^{I}) to an organic halide generates a free radical which rearranges to give cyclised product (Eqns. 7-9):



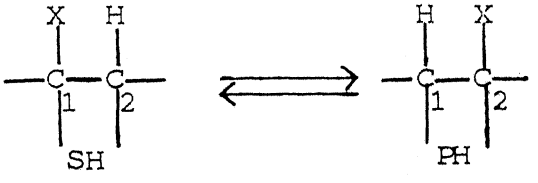




1.7 B_{12} Biochemistry: Cobaloxime as Model

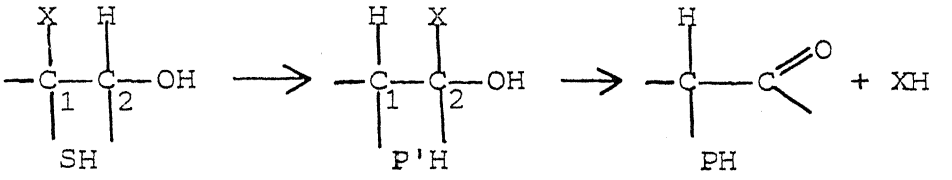
Organocobalt complexes in spite of their wide structural differences to coenzyme B_{12} show many electronic, electrochemical and chemical similarities to the latter and its derivatives. Our understanding of the chemistry of vitamin B_{12} coenzyme, as it stands today, is largely an outcome of the study of its model compounds. Some aspects of the relationship of B_{12} model to B_{12} biochemistry have recently been reviewed.[34,229] Prior to a consideration of the relevance of cobaloxime chemistry to B_{12} biochemistry, it is worthwhile to highlight some aspects of the latter.

In vitamin B_{12} mediated enzymatic reactions the corrinoids act in association with a protein. Thus, corrinoids are the co-factors or coenzymes for all these enzymatic processes which can be divided into two sub-groups;[151,230] those mediated by i) methylcobalamin and ii) 5'-deoxyadenosylcobalamin (A-Co^{III}). Our interest lies particularly in the latter in which the reactions catalysed by coenzyme B_{12} appear to be diverse and they all can be categorized as vicinal 1,2-H interchange (Eqn. 10 or 11):



.. (10)

(X = NH_2, COSCoA, $C(=CH_2)CO_2^-$, $CH(NH_3^+)CO_2^-$)



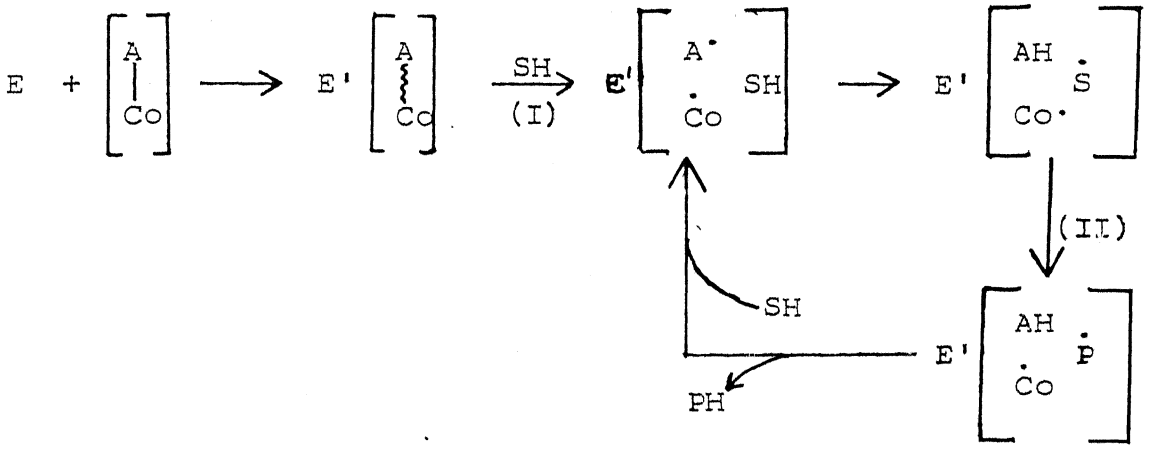
.. (11)

(X = OH or NH_2)

The overall mechanism of such process has been proposed by many as outlined in Scheme 1.9.[108] The steps of interest are: (I) Co-C bond cleavage and (II) the rearrangement step of the substrate ($\dot{S}$) to the product ($\dot{P}$):

Scheme 1.9

Simplified description of B_{12} dependent catalysis



[E = apoenzyme; Co-A = coenzyme B_{12}; E' [] = conformationally changed enzyme and its active site pocket; Co⌒A = conformationally changed coenzyme with a weakened Co-C bond; Co = B_{12r}; A = 5'-deoxyadenosyl radical enzyme bond; $\dot{S}$ and $\dot{P}$ are substrate and product radicals.]

(I) Co-C bond cleavage step and organocobaloximes

It is suggested that coenzyme B_{12} acts as an organic radical carrier.[231] Thus, upon mixing a B_{12}-dependent enzyme (such as dioldehydrase) with coenzyme, conformational changes take place both in enzyme and coenzyme, which then 'triggers' the Co-C bond cleavage.[77,116,232-244] Unfortunately, no direct information exists on the nature of the conformational changes of the coenzyme. Various possibilities[229,231,237-242] which may contribute to the cleavage include:

(a) Enzyme induced corrin distortion which increases the steric interaction with 5'-adenosyl ligand (5'-AdO);

(b) A change in the position of benzimidazole which induces a corrin distortion as in (a);

(c) A corrin distortion which lengthens the Co-N (benzimidazole) bond;

(d) A direct lengthening or shortening of the Co-C bond; and

(e) Direct lengthening or angular distortion of the Co-C bond.

Of course, combination of effects are also possible. An evaluation of the above possibilities (a-e) with respect to cobaloximes as model is illustrated below.

(a) This effect may be attributed[77,232,233,235,237-242] to a steric cis-influence of the 5'-AdO to the corrin chromophore resulting in a corrin distortion followed by a Co-C bond weakening. This is best illustrated from the structural parameter

of $RCo^{III}(dmgH)_2PPh_3$ (1, R = i-Pr; R = 2-butyl). A significantly large Co-C bond and greater distortion of $(dmgH)_2$ ring in (1) compared to (2) leads to a conclusion that packing forces definitely modulate the distortion. That such a lengthening of Co-C bond affects the Co-C bond energy is further evident from the apparent instability of isoproyl-cobalamin.[242]

(b) The benzimidazole in coenzyme B_{12} lies over six membered chelate rings and the Co-N(3)-C angles are unsymmetrical to avoid contact of the benzimidazole six membered ring with the corrin. Any distortion which moves the benzimidazole over the five membered chelate ring[245] or increases interaction of the benzimidazole six membered ring with corrin can induce a change in corrin pucker which can weaken the Co-C bond by enhancing repulsive interactions between the corrin and the 5'-deoxyadenosine. No crystallographic evidence currently exists for this type of relationship, although the relationship of the orientation of planar L ligands with respect to the size of the equatorial chelate rings has been considered.

(c) The most clear cut relationship between Co-C bond energy and a structural parameter is that between the Co-C bond strength and the axial Co-N bond length.[236,245] This relationship points out that a lengthening of the Co-N bond by a corrin distorition could also promote Co-C bond cleavage. A good axial donor stabilizes the Co(III) oxidation state and

lengthening of the Co-N bond decreases electron donation and destabilizes (Co^{III}).[243,244]

(d) If, via interaction of the benzimidazole side chain with the enzyme, the conformational change involves a lengthening of the Co-N bond, the Co-C bond cleavage will be favoured. Conceivably, Co-N bond shortening by a similar process can weaken the Co-C bond by a direct trans influence.[108]

(e) Work with substituted R groups[234-236,246] reveals that the Co-C bond can be stretched easily, which the enzyme may be able to do directly. Rather, large distortion of Co-C_α-C_β bond angles have been found in neopentyl cobaloximes[234] whereas neopentyl derivatives of cobalamin are rather unstable.[241,247-259]

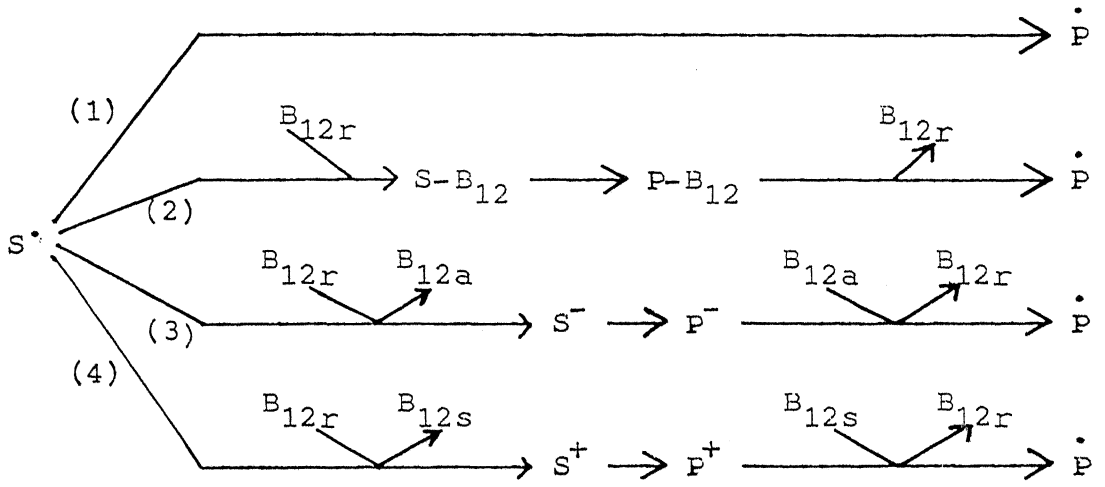
(II) Rearrangement step and organocobaloximes

The least well understood and most controversial aspect of Scheme 1.9[108] is the substrate rearrangement step (II).[250-252] The conversion of the substrate radical $\dot{S}(-\overset{X}{\underset{1}{C}}-\underset{2}{\dot{C}}-)$ to the product radical $\dot{P}(-\underset{1}{\dot{C}}-\overset{X}{\underset{2}{C}}-)$ may follow either free radical or ionic pathways with or without the participation of cobalamin cofactor (Scheme 1.10).[116]

Preliminary proof for (1) has been afforded by Halpern et al. for methylmalonyl Co-A mutase reaction.[253] It is emphasized that the only role of coenzyme B_{12} in these reactions is tha of a free radical precursor.

Scheme 1.10

Alternative pathways for substrate radical rearrangement



The alternative mechanism (2) involving the intermediacy of organocobalt adduct has been proposed by many workers on non-enzymatic model studies in a number of B_{12} dependent transformations. The studies carried out by Rétey et al.[106,254] and Tada et al.[255,256] on methyl malonylcoenzyme mutase is particularly noteworthy. The role of cobalt moiety has been attributed to induce steric strain around the migrating group and thus induce rearrangement.[188]

The ionic pathways (3) and (4)[77] lack direct evidence for the intermediacy of the vitamin B_{12s} (Co^I) in all B_{12} dependent reactions so far.[89,257-260] However, recent studies by Finke et al.[252] on diol dehydrase process are noteworthy. Their model considers a cobalt independent S^+ to P^+ transformation and also for the first time takes into account

the protein bound substrate and coenzyme.

In summary following understanding from above details can be drawn:

i) Co-C bond is extremely susceptible to facile dissociation conclusively homolytically.[144,244,261]

ii) Steric factors play an important role in weakening the Co-C bond.[262]

iii) Transformation of the substrate is possible, depending totally on the choice of the model system.

iv) Reaction pathways are still open to question and influence of external parameters are still to be understood. However, several reasonable alternatives exist for the nature of conformational change and reaction pathways. More work is required in both model systems and enzymes in order to define the nature of the most important effects.

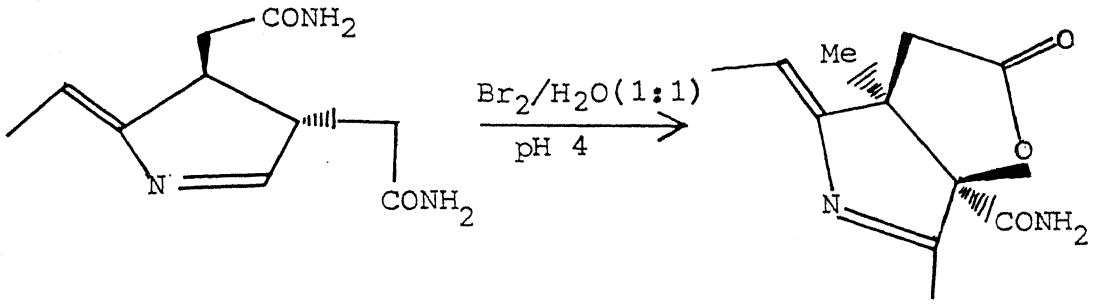
1.8 Electrophilic Substitution in Vitamin B_{12}

Electrophilic attack in vitamin B_{12} corrinoids can be visualised on two centres.

A. Electrophilic substitution on the corrin chromophore:

Electrophilic reagents (H^+, Cl^+, Br^+, NO_2^+) with corrinoids give 10-substituted derivatives. However, with halogenating agents, depending upon the conditions and type of corrin, formation of C-lactone is shown to be an alternative reaction

pathways:



Recently, an additional complication with halogenating reagents was observed;[263] for example, chlorination of cobester* gives within seconds a colourless adduct having six chlorine atoms substituted at different positions.

Direct methylation of corrin chromophore is not possible. Successful substitution is achieved only with two reagents[151] $(SCN)_2$ and $ClCH_2OCH_2Ph$.

B. Electrophilic attack on Co-C bonds:

The Co-C bond of alkyl corrinoids can be cleaved by halogenating reagents. However, the mechanism of this reaction is controversial.[264]

$$\text{Ado-Cbl} + I_2 \longrightarrow \text{I-Cbl} + \text{AdoI}$$

In a recent study, aqueous solution of iodine reacts with aqueous solution of methylcobalamin to give aquocobalamin and methyl iodide, while in the presence of chloride ion the product

---

*cobester = heptamethyl cobyrinic acid

is methyl chloride. It is proposed that the initial step is the electron transfer from the cobalamin to iodine to form the radical cation of the methylcobalamin which subsequently undergoes a nucleophile induced heterolytic cleavage of the Co-C bond.[265]

Methylcobalamin (Mecbl) undergoes a bimolecular electrophilic substitution (S_E2) with Hg(II) to give methylmercury ion[266] as mentioned earlier (p.45). Some of the reactions of methylcobalamin with Pd(II) chloride are mechanistically similar to the reaction of Hg(II). However, Cr(II) affects a reductive cleavage of Co-C bond of RCbl according to the following stoichiometry:[181]

$$RCbl + Cr(II)(aq.) \longrightarrow Cbl(II) + RCr^{II}(H_2O)_5 \xrightarrow{H^+} RH + Cr^{III}(aq.)$$

The mechanism of this cleavage is either S_H2 or redox S_E2.

1.9 Scope of the Present Work

The discussion presented in this chapter so far, clearly points to the fact that organocobaloximes, over the past two decades have enlightened three broad, but interrelated spectrum of research namely,

i) synthesis of complexes having stable cobalt-carbon bond,

ii) non-enzymatic studies on model compounds in elucidating the mechanism of B_{12}-dependent enzymatic reactions,

iii) Studies on a number of interesting organometallic reactions originating from the homolytic and heterolytic cleavage of cobalt-carbon bond which is being recognized as an independent area of research altogether.

iv) Studies aimed to explore the synthetic usefulness of B_{12} model compounds in general and organocobaloximes in particular.

However, in view of the relatively poor understanding of the intricacies involved in B_{12}-catalytic chain; world wide research effort in all the four areas are being pursued with equal vigour.

In vitamin B_{12} coenzyme catalysed enzymatic reactions the involvement of both homolytic as well as heterolytic pathways is possible. Though homolytic pathway is very well studied in literature, the role of heterolytic pathway, is only recently recognized. It is anticipated therefore, that the study of organocobaloximes with a particular emphasis on the cleavage of Co-C bond by heterolytic pathway will be quite useful.

Keeping this in mind, we have taken up the following study. Since halogens and pseudohalogens are known to be the effective reagents to cleave the metal to saturated carbon bond, such a study is taken up for benzyl and substituted benzyl cobaloximes with halogens (Cl_2 , Br_2 , I_2 , ICl) and pseudohalogen $(SCN)_2$. The particular emphasis of the study is to

understand the precise mechanism of Co-C bond cleavage. Besides, a carefully designed set of cobaloximes are synthesized in order to understand the phenomenon "Co-C bond cleavage versus ring halogenation" and its implication to gain further insight in mechanistic study. The work has been described in Chapters 2 and 3.

Chapter 2

ORGANOCOBALOXIMES: HALOGENOLYSIS – A MECHANISTIC STUDY

2.1 Background

Transition metals are known to have a marked effect on the reactions of organic molecules to which they are π bonded.[267] However, much less is known about the influence of σ bonded transition metals on organic reactivity, both in direction and degree. In the field of σ bonded organotransition-metal complexes, the variety of ligands often required to stabilize the carbon-metal bond, ensures that such complexes are frequently polyfunctional molecules containing groups of widely different character, atoms of significantly different electronegativity and any of a range of possible charges. The highest occupied molecular orbital, which usually plays a vital role in these reactions, may be located on the metal, on one of the ligands, or in metal-ligand bonds.[152]

Studies of mechanism have provided valuable information about ways in which carbon-metal bond may be cleaved. The mechanism through which cobalt-carbon bonds are cleaved and the factors that promote (or inhibit) such cleavage, are of considerable importance.

Three limiting mechanisms can be formulated for bond cleavage leading to the release of Co^{III}, Co^{II} or Co^{I}. These processes are depicted in Equations (1, 2, 3) where $[R^-]$, $[R^\cdot]$, $[R^+]$ may represent free species or bound forms:

$$(Co^{III})\text{-}R \longrightarrow (Co^{III}) + [R^-] \quad \ldots (1)$$

$$(Co^{III})\text{-}R \longrightarrow (Co^{II}) + [R^\cdot] \quad \ldots (2)$$

$$(Co^{III})\text{-}R \longrightarrow (Co^{I}) + [R^+] \quad \ldots (3)$$

Besides, oxidative and reductive Co-C bond cleavage is also known.

For any particular pair of reagents, an electrophile and an organometallic substrate, one may anticipate three main types of primary reactions: displacement reaction, Lewis acid/base complex formation, and electron transfer, which are unlikely to be restricted to a single definable site and each may have a variety of possible consequences.

In the mechanism of the σ bonded substrates with electrophiles, the main emphasis is in terms of the degree of change

of carbon-metal bond in the primary reaction step and the site of primary attachment of the electrophile to the substrate. Reaction possibilities are: synchronous attack of the electrophile with cleavage of carbon-metal bond, reactions in which the carbon-metal bond is modified, reactions in which there is little influence of or on the carbon metal bond. Though in principle synchronous cleavage of carbon-metal bond may also occur when electrophile attacks at centers other than α-carbon, there is an appreciable tendency in such cases for the carbon-metal bond moiety to be modified. Electrophilic attack on the metal is thus formally a two electron oxidation process liable to induce subsequent free radical reactions and is difficult to distinguish from other oxidative processes involving electron transfer. Similarly, there are many reactions of electrophiles with organometallic complexes which donot involve substantial changes in the character of the carbon-metal bond. These are, (a) reactions of ligands at positions remote from and barely influenced by metal, and (b) reactions which cause sufficient change in the electronic character of the metal to influence the rate of subsequent reactions at the carbon-metal bond.

Among several types of σ-bonded organotransition complexes, the organopentachromium(III) ions offer by far, the most clean reactions with electrophiles.[85,267-171] In sharp contrast, the most interesting, yet less understood substrates include the organocobalt(III) and organoiron(III) complexes.

This is because of the seemingly endless variety of reactions they undergo, and in case of organocobalt complexes, their importance in relation to the chemistry of coenzymes B_{12}.[34] The reactions of mercury metal ions with organocobalt(III) complexes have been studied[272] in great detail especially, because of their relevance to biomethylation and a more comprehensive picture has been obtained in this respect. However, the halogenation studies have resulted in no unified understanding so far. Even for other transition, and non-transition organometallics like carbon-tin,[273] carbon-mercury,[274] the halogenation studies have provided only qualitative information on the metal-carbon bond cleavage.

Halogenation of organocobaloximes, in particular, has been confined mainly to alkylcobaloximes and their reaction with ICl and I_2[33,152,154,275,276] and their mechanistic elucidations are attempted from kinetic considerations only.[203] In comparison, the halogenation of benzyl cobaloxime appears to be more complicated and has not been studied systematically in detail. Several mechanisms for Co-C bond cleavage are known: (i) direct electrophilic substitution on the α carbon, (ii) direct radical attack on α carbon, (iii) oxidative dealkylation process, (iv) single electron transfer mechanism. Additional feature of benzyl cobaloxime is that the benzene ring is also susceptible to electrophilic substitution. Each one of these mechanisms find support from the literature. However,

no clear cut one mechanism has emerged so far.

It is, therefore, desirable to look into this problem in a systematic way so that a differentiation between the above mechanisms can be made.

In the present study, a carefully designed set of substituted benzylcobaloximes are synthesized so that,

i) the substituent effect of $-CH_2Co^{III}(dmgH)_2Py$ group can be estimated,

ii) unambiguous evidence in support of a most reasonable mechanism can be made,

iii) the aromatic ring is sufficiently activated for ring halogenation in preference to Co-C cleavage,

iv) a clear differentiation between inductive and mesomeric effect on the Co-C cleavage can be reached at.

2.2 Experimental

All reactions were carried out in oven dried (100-120°C) apparatus. Magnetic stirring was provided unless otherwise stated to the reaction procedures. Perfit rotary evaporator was used for concentrating the reaction mixture. Distilled water was used in all aqueous workups.

Solvents and gases

Commercial grade solvents were used after distillation. 40-60°C, 60-80°C fractions of petroleum ether were commonly

used. Chloroform and dichloromethane were distilled from phosphorus pentoxide and kept over molecular seives 4 Å type. Methanol and ethanol were distilled from calcium oxide. Benzene, toluene and carbon tetrachloride were kept over calcium chloride and distilled after decantation. Distilled benzene and toluene were kept over sodium wire. Sodium dried diethyl ether and tetrahydrofuran were further distilled from lithium aluminium hydride or calcium hydride prior to use. Tetrahydrofuran was kept over calcium hydride. Pyridine was distilled from potassium hydroxide and stored over potassium hydroxide pellets.

Extra pure IOL AR-2 (impurity 2 ppm) dinitrogen was used and purified by passing through traps of Fieser's solution, conc. sulphuric acid and potassium hydroxide pellets. Dioxygen gas was used directly from the cylinder.

Chromatography

Small plates suitable for preliminary exploration of the chromatographic process with regard to the selection of solvent for preparative chromaplate or for monitoring reaction process were prepared from microscopic slide using Merck silica gel-G. For preparative chromaplate silica gel-G or alumina (neutral) were used. Flash column chromatography was often used using silica gel-G and handy-aspirator. Visualization of spots or bands were effected by exposure to iodine vapour generally.

Gas liquid chromatography was employed for the rapid and convenient analyses of the composition of mixtures of organic compounds (comparing with authentic samples) on Shimadzu chromatograph GC-9A using SE-30 column.

Iatroscan TH-10 was used for getting the ratios of the organic product mixture.

Physical measurements and instruments used

Melting points (m.p.) were determined on Fisher-Johns melting point apparatus and are uncorrected. Boiling (b.p.) are also uncorrected.

Infrared (IR) spectra were recorded on Perkin-Elmer model 3220 and 850 infrared-grating spectrophotometers and are reported in wave numbers (cm^{-1}). Electronic spectra were recorded on Cary-17D and Shimadzu UV-190 double beam spectrophotometers.

Proton magnetic resonance (^1H NMR) spectra were recorded on 80 MHz (Bruker WP-80), 200 and 400 MHz (Bruker WH-200 and WH-400), 90 and 100 MHz (Varian EM-390 and HA-100) spectrometers.

Chemical shifts are reported in ppm downfield from internal references TMS (δ). Multiplicity is indicated using following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), etc.

Coupling constants are reported wherever necessary and are expressed in Hertz (Hz).

Mass spectra were recorded at Regional Sophisticated Instrument Centre, Lucknow on VG Micromass 7070F mass spectrometer. Principal molecular fragments are reported.

Electrochemical measurements were done with the help of a PAR model 370-4 electrochemistry system incorporating the model 174-A polarographic analyser and model 377-A cell system using a platinum electrode and standard calomel electrode (SCE) in acetonitrile (0.1 M TEAP). Reported potentials are uncorrected for junction contributions. Because of its lower residual current, experiments were conducted at pH 2 and at concentrations ca. 10^{-4} to 10^{-3} mol/lit.

Carbon, hydrogen and nitrogen analyses were carried out at Central Microanalytical Lab., I.I.T., Kanpur and Regional Sophisticated Instruments Centre (CDRI), Lucknow.

Starting materials

4-Acetamidobenzaldehyde, anhydrous aluminium chloride, 3-anisic acid, benzoyl peroxide, benzyl chloride, borontrifluoride (ether), t-butyl alcohol, bromobenzene, bromine, 4-chlorobenzyl chloride, 4-cresol, cumene, cupric chloride, cobalt(II) chloride, carbon disulphide, dimethylglyoxime, dimethylsulphate, lithium aluminium hydride, lithium chloride, 4-nitrotoluene, oxalic acid, ortho-phosphoric acid, para-formaldehyde, phosphorus pentachloride, pyridine, red-phosphorus, sodium borohydride, sodium potassium tartarate, sodium hydride, sulphuryl

chloride, tetramethylammonium chloride, tetramethylammonium bromide, thionyl chloride, 4-tolualdehyde, thiophenol, 4-toluonitrile, 4-toluicacid, tosylchloride, meta- and para-xylene were commercial materials (mostly Aldrich) and in general were either distilled or recrystallized before use.

Halogens: Bromine, iodine were commercial materials. Chlorine gas was generated from the reaction of conc. hydrochloric acid with potassium permanganate and was passed through water and conc. sulphuric acid trap before absorbing into chloroform or glacial acetic acid.

Iodine monochloride was prepared by treatment of iodine with dry chlorine at ambient temperature and was distilled before use.

2.2.1 Synthesis of Organic Precursors

The preparative routes for organic precursors are outlined in Scheme 2.1 (p. 85) and are described below.

Preparation of 4-methyl benzyl chloride (1)[277]

A mixture of p-xylene (10.0 g), sulphuryl chloride (9.0 g) and benzoyl peroxide (0.05 g) in dry carbon tetrachloride (25 ml) was heated to reflux for two hours. Excess p-xylene and carbon tetrachloride were removed and the residue was distilled to give 4-methyl benzyl chloride (10.5 g, 79%), b.p. 92°/20 mm (lit.[277] b.p. 92°/20 mm).

^{1}H NMR ($CDCl_3$), δ (ppm): 7.28-6.95 (m, Ph), 4.48 (s, $-CH_2$), 2.31 (s, CH_3).

Preparation of 4-isopropyl benzyl chloride (2)[278]

A mixture of cumene (51.0 g), para-formaldehyde (15.4 g), glacial acetic acid (40.0 ml), hydrochloric acid (46.7 ml) and 85% ortho-phosphoric acid (23 ml) was heated to reflux for 24 hours. On cooling, organic layer was separated, washed with water and dried over magnesium sulphate. Distillation of crude mixture gave cumene (30 ml) and 4-isopropylbenzyl chloride (16.0 g, 56%), b.p. 94°C/5.8 mm (lit.[278] b.p. 88°C/5.5 mm).

^{1}H NMR ($CDCl_3$), δ (ppm): 7.0 (s, Ph), 4.4 (s, $-CH_2$), 2.55-3.2 (m, -CH), 1.25 (d, CH_3).

Preparation of 4-tert-butyl benzyl chloride (3)[279]

tert-Butyl chloride was prepared using tert-butanol and hydrochloric acid. Friedal craft alkylation was done using benzene and tert-butyl chloride to give tert-butyl benzene. tert-Butyl benzene (9.6 g), para-formaldehyde (2.9 g), glacial acetic acid (7.5 ml), conc. hydrochloric acid (8.8 ml) and 85% ortho-phosphoric acid (4.3 ml) were heated to reflux at 150°C for 20 hours. Reaction was worked up in the same manner as above for compound number (2), yield (1.8 g, 58%); b.p. 88°C/3 mm (lit.[279] b.p. 114.5°C/10 mm).

^{1}H NMR ($CDCl_3$), δ (ppm): 7.2 (s, Ph), 4.46 (s, $-CH_2$),

1.3 (s, $-CH_3$).

Preparation of 4-bromobenzyl bromide (4)[280]

Bromine (10.2 g) was added dropwise during 30 minutes with irradiation to 4-bromotoluene (10.2 g) at 120°C. Stirring was continued for two hours. The product which got solidified on cooling was filtered and washed with ethanol (3 x 10 ml). The product was recrystallized using light petroleum ether: benzene (80:20) mixture. Yield (9.8 g, 65%); m.p. 61°C (lit.[280] m.p. 61°C).

^1H NMR ($CDCl_3$), δ (ppm): 7.1-7.5 (m, Ph), 4.38 (s, $-CH_2$).

Preparation of 4-nitrobenzyl bromide (5)[281]

Bromine (36.8 g) was added dropwise during two hours to 4-nitrotoluene (30.0 g) at 150°C. Reaction mixture was poured into petroleum ether (60-80°C) (400 ml). The crude product was recrystallized using benzene:petroleum ether mixture (50:50). Yield (22.0 g, 88%); m.p. 96°C (lit.[281] m.p. 97.5-99.0°C).

^1H NMR ($CDCl_3$), δ (ppm): 7.35-8.20 (m, Ph), 4.5 (s, $-CH_2$),

Preparation of 4-cyanobenzyl bromide (6)[282]

4-Toluonitrile (14.6 g, in 50 ml carbon tetrachloride) was added dropwise to a suspension of N-bromosuccinimide (18.0 g, in 50 ml carbon tetrachloride) and benzoyl peroxide (0.3 g).

Reaction mixture was heated to reflux for two hours. The solution was filtered hot and the filtrate was evaporated to half its volume. Crude product was recrystallized from ethanol (14.0 g, 80%), m.p. 114°C (lit.[282] m.p. 116°C).

^{1}H NMR ($CDCl_3$), δ (ppm): 7.5-7.8 (m, Ph), 4.52 (s, $-CH_2$).

Preparation of 4-bromomethyl benzoic acid (7)[283]

Bromine (16.0 g) was added dropwise over a period of 2.5 hours to a refluxed solution of 4-toluic acid (11.1 g) in benzene (200 ml). The solution was irradiated with 200 W tungsten lamp. The solid product separated out on cooling was recrystallized from ethyl acetate (14.3 g, 66%), m.p. 226°C (lit.[283] m.p. 227.5°C).

^{1}H NMR ($CDCl_3$ + DMSO-d_6), δ (ppm): 7.38-8.1 (m, Ph), 4.58 (s, $-CH_2$), 2.6 (br, OH).

Preparation of 4-bromomethyl benzaldehyde (8)[284]

Bromine (25 ml) was added dropwise to red-phosphorus (6.2 g) in carbon disulphide (60 ml) with cooling followed by 4-tolualdehyde (16.0 g). The mixture was heated to reflux for two hours. On cooling, water (100 ml) was added. Carbon disulphide layer was separated, washed with water, and dried over calcium carbonate. Carbon disulphide layer was distilled off and the crude product, 4-methyl benzil bromide, thus obtained was purified using ethanol and active charcoal (12.0 g, 60%), m.p. 62°C

(lit.[284] m.p. 62°C). This was further brominated at 140°C with uv irradiation giving w,w,w'-tribromoparaxylene (10.9 g, 70%), m.p. 104°C (lit.[284] m.p. 106°C).

Dry oxalic acid (2.5 g) was added in small portion to w,w,w'-tribromoparaxylene (5.7 g) at 150-160°C. Reaction mixture was further heated for 1.5 hours. On cooling, the reaction mixture was extracted with ethanol and crude product was purified using ethanol-water and active charcoal. The product was recrystallized using petroleum ether (3.0 g, 72%), m.p. 92°C (lit.[284] m.p. 95.3°C).

^{1}H NMR ($CDCl_3$), δ (ppm): 6.95-8.0 (m, Ph), 4.52 (s, $-CH_2$), 9.8 (s, CHO).

Preparation of 4-methoxy benzyl bromide (9)[285]

4-Methyl anisole (12.2 g), b.p. 172°C, obtained by the alkylation of p-cresol with dimethyl sulphate, was brominated with N-bromosuccinimide (14.4 g) in carbon tetrachloride (60 ml). After usual workup, the residue was distilled to give 4-methoxy benzyl bromide (12.5 g, 60%), b.p.110°C/2 mm.(lit.[285] b.p. 110-113°C/2 mm).

^{1}H NMR ($CDCl_3$), δ (ppm): 6.74-7.3 (m, Ph), 4.5 (s, $-CH_2$), 3.8 (s, -OMe).

Preparation of 4-acetamidobenzyl chloride (10)[286]

4-Acetamidobenzyl alcohol (12.0 g, m.p.123°C; ^{1}H NMR ($CDCl_3$), δ (ppm): 7.1-7.4 (m, Ph), 4.36 (s, br, $-CH_2$), 3.1 (br, OH), 2.5 (br, -NH), 2.2 (s, $-CH_3$)) obtained by sodium borohydride reduction of 4-acetamidobenzaldehyde, was treated with thionyl chloride (9.6 g) in dry benzene (60 ml). The reaction mixture was heated to 80-90°C for ten minutes. The crude product after evaporation of excess thionyl chloride and benzene was recrystallized from petroleum ether (3.0 g, 22%), m.p. 151-154°C (lit.[286] m.p.155°C).

^{1}H NMR ($CDCl_3$), δ (ppm): 7.18-7.56 (m,Ph), 4.5 (s, $-CH_2$), 2.6 (br, -NH), 2.2 (s, $-CH_3$).

Preparation of 4-dimethylaminobenzyl tosylate (11)[287]

4-Dimethylaminobenzyl alcohol (b.p. 125°C/1 mm; ^{1}H NMR ($CDCl_3$), δ (ppm): 6.52-7.22 (m, Ph), 5.16 (br, -OH), 4.42 (s, CH_2), 2.9 (s, CH_3)) was obtained in 90% yield by the lithium aluminium hydride reduction of 4-dimethylaminobenzyldehyde. Tosylation was carried out as follows: 4-Dimethylamino benzyl alcohol (2.0 g, in 20 ml THF) was added dropwise over two hours to sodium hydride (1.1 g in 10 ml THF) at 0°C under nitrogen. After stirring for further two hours, the temperature was brought down to -40°C. Tosyl chloride (2.5 g in 20 ml THF) was added very slowly over a period of five hours maintaining the temperature at -40°C.

The mixture was allowed to stand at 0°C overnight. It was poured into ice water and the organic product was extracted with THF (3 x 10 ml) and washed with brine solution. The organic layer was dried over anhydrous magnesium sulphate. Evaporation of THF at 0°C under vacuum afforded tosylate (11) as yellow oil (3.5 g).

^{1}H NMR ($CDCl_3$), δ (ppm): 6.46-7.7 (m, Ph), 4.45 (s, $-CH_2$), 2.85 (s, $N(CH_3)_2$), 2.35 (s, $-CH_3$).

Preparation of 3-methyl benzyl chloride (12)[288]

m-Xylene (7.4 g, in 50 ml carbon tetrachloride) was refluxed with sulfuryl chloride (2.8 g) and benzoyl chloride (0.2 g) for an hour. Solvent and excess m-xylene were distilled off. Residue on fractionation gave 3-methyl benzyl chloride (5.4 g, 54%), b.p. 65°C/5 mm (lit.[288] b.p. 65°C/5 mm).

^{1}H NMR ($CDCl_3$), δ (ppm): 7.18 (m, br, Ph), 4.5 (s, $-CH_2$), 2.38 (s, $-CH_3$).

Preparation of 3-methoxy benzyl bromide (13)[289]

3-Methoxy benzyl alcohol (10.0 g) (b.p. 129°C/9 mm), obtained in 90% yield by lithium aluminium hydride reduction of 3-anisic acid, was treated with phosphorus tribromide (10.6 g) in dry ether (200 ml). Reaction mixture was kept at room temperature for 16 hours and then hydrolyzed with ice water.

After usual workup the ethereal layer was dried over anhydrous magnesium sulphate and was evaporated. The residue on distillation gave 3-methoxy benzyl bromide (13.0 g, 90%), b.p. 124°C/13 mm (lit.[289] b.p. 123°C/13 mm).

^{1}H NMR ($CDCl_3$), δ (ppm): 6.60-7.22 (m, Ph), 4.4 (s, $-CH_2$), 3.65 (s, $-OCH_3$).

Preparation of chloromethyl phenyl sulphide (14)[290]

Thioanisole (8.4 g)((b.p. 188°C); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.2 (s, br, Ph), 2.46 (s, CH_3)) obtained by the alkylation of thiophenol with dimethyl sulphate, was treated with sulphuryl chloride (9.0 g) in dichloromethane (50 ml). The mixture was refluxed for 3 hrs. After usual workup, the residue was distilled to give chloromethyl phenyl sulphide (10.0 g, 94%), b.p. 66°C/2 mm (lit.[290] b.p.103-104°C/12 mm).

^{1}H NMR ($CDCl_3$), δ (ppm): 7.3 (s, Ph), 4.82 (s, $-CH_2$).

Preparation of chloromethyl phenyl ether (15)[291]

Sodium sulphite (252.0 g), dichloromethane (64 ml), ethanol (30 ml) water (500 ml) and cupric chloride (5.0 g) were heated in an autoclave at 100°C for 30 hrs. The reaction mixture was dried on steam bath and residue was subjected to soxlet extraction with ethanol giving chloromethyl sodium sulphonate (130 g, 85%).

Chloromethyl sodium sulphonate (100.0 g), phenol (70.0 g), sodium hydroxide (27.0 g) and water (10 ml) were heated for four hours at 200-220°C. The reaction mixture was cooled, diluted with water and further heated on steam bath. Reaction mixture was filtered and residue was washed with ether. pH of filtrate and washing was adjusted to 5. Evaporation of solvent gave rise to phenyloxymethane sulphonate (85.0 g, 61%).

Phenyloxymethane sulphonate (50.0 g) was treated with phosphorus pentachloride (100.0 g). The resulting oily mixture was poured into ice-water mixture and extracted with ether, washed with 1 N NaOH, dried over magnesium sulphate and distill-ed to give phenyl chloromethyl ether (26.0 g, 77%), b.p. 57°C/0.5 mm (lit.[291] b.p. 39°C/0.2 mm).

^{1}H NMR ($CDCl_3$), δ (ppm): 7.3 (m, Ph), 5.82 (s, $-CH_2$).

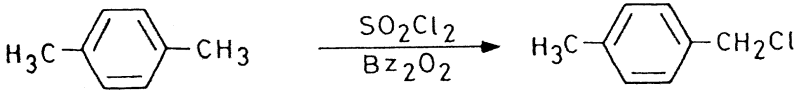
2.2.2 Synthesis of Cobaloximes

The cobaloximes were prepared by methods S.1, S.2, S.3 and S.4 as described below:

Chloro(pyridine)cobaloxime(III)[37] (16)

Pyridine (3.6 g) was added to a hot solution of cobalt(II) chloride hexahydrate (5.0 g, 21 mmol) and dimethylglyoxime (5.5 g, 47 mmol) in 95% ethanol (200 ml). After cooling to room temperature, a stream of air was blown through the solu-tion for 0.5 hr. The product (16) was allowed to crystallize out from solution which was filtered, washed successively with

Scheme 2.1



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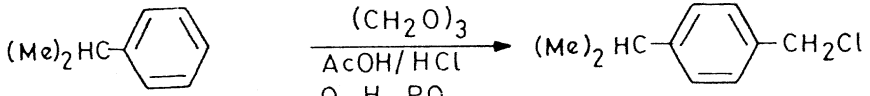

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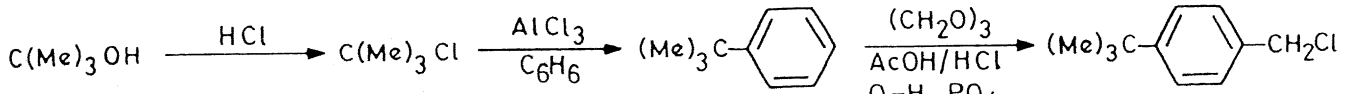

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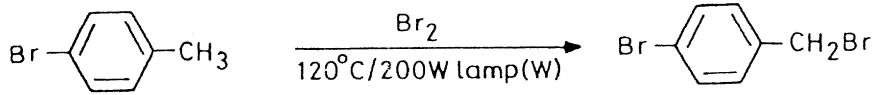

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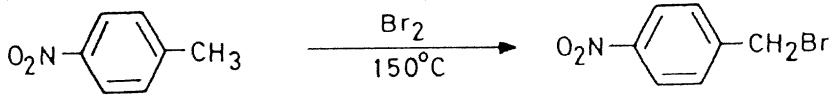

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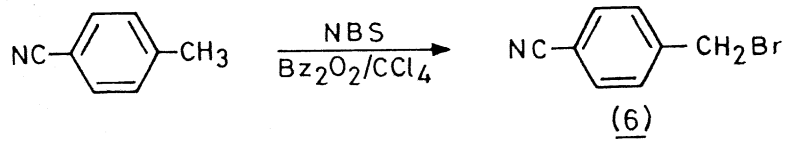
Scheme 2.1 (contd.)



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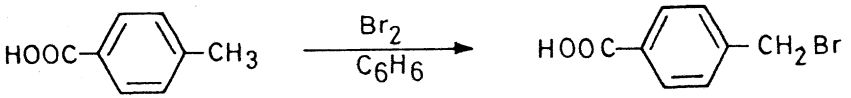

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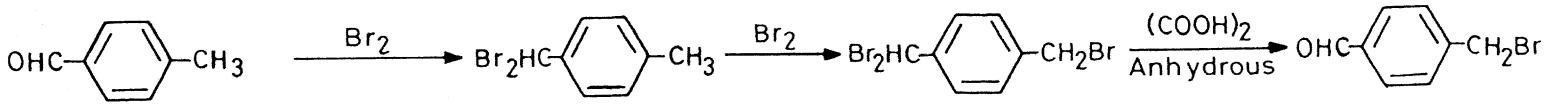

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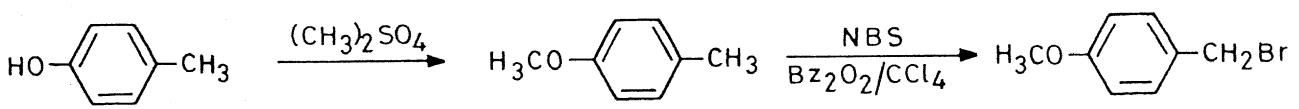

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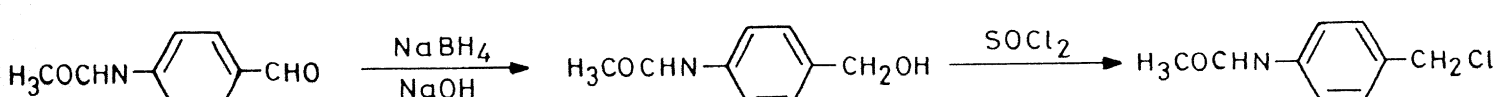

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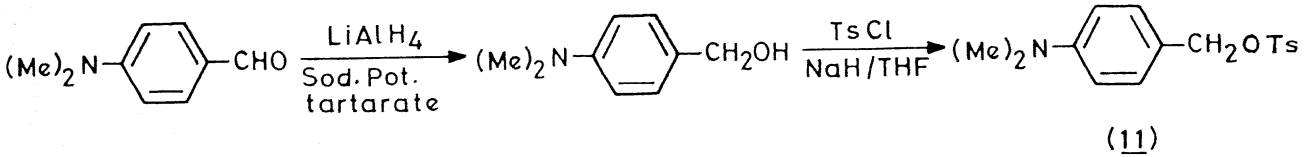

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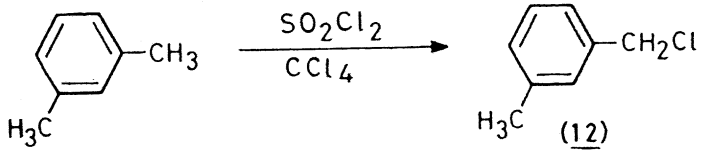

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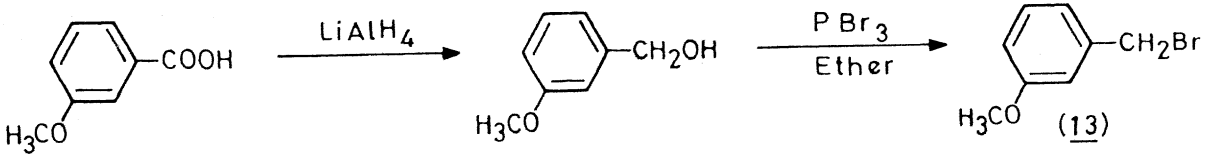

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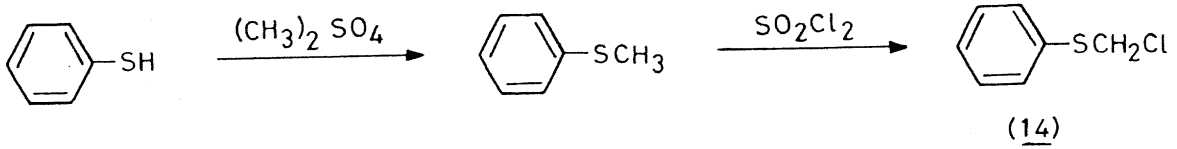

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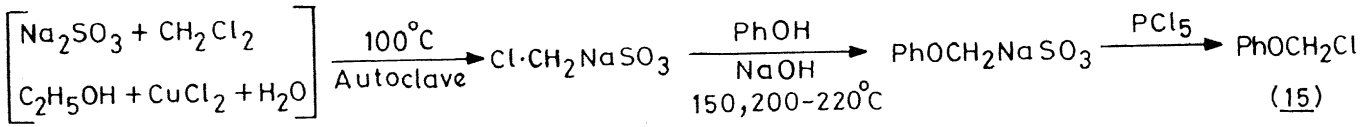


(15)

Scheme 2.1 (contd.)

$$Co^{I}(dmgH)_2\,Py + RX \xrightarrow[MeOH]{N_2} RCo^{III}(dmgH)_2\,Py$$

R= 17) $PhCH_2$ —

18) $4\text{-}CH_3C_6H_4CH_2$ —

19) $4\text{-}i\text{-}C_3H_7C_6H_4CH_2$ —

20) $4\text{-}t\text{-}C_4H_9C_6H_4CH_2$ —

21) $4\text{-}BrC_6H_4CH_2$ —

22) $4\text{-}ClC_6H_4CH_2$ —

23 $4\text{-}CNC_6H_4CH_2$ —

24) $4\text{-}CHOC_6H_4CH_2$ —

25) $4\text{-}COOHC_6H_4CH_2$ —

26) $4\text{-}NO_2C_6H_4CH_2$ —

27) $4\text{-}NHCOCH_3C_6H_4CH_2$ —

28) $4\text{-}NMe_2C_6H_4CH_2$ —

29) $4\text{-}CH_3OC_6H_4CH_2$ —

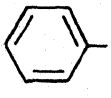
30) $3\text{-}CH_3C_6H_4CH_2$ —

31) $3\text{-}CH_3OC_6H_4CH_2$ —

32) $C_6H_5SCH_2$ —

33) $C_6H_5OCH_2$ —

[X = Cl, Br, Ts]

$$HCo(dmgH)_2\,Py + C_6H_5NH_2 + HCHO \xrightarrow{H_2} \text{  }\text{-}NHCH_2Co^{III}(dmgH)_2\,Py$$

water, ethanol and ether and dried at room temperature *in vacuo*, (5.0 g, 58%, based on cobalt(II) chloride hexahydrate).

^{1}H NMR ($CDCl_3$), δ (ppm): 2.35 (s, CH_3), [8.25 (α, d, Py), 7.26 (β, m, Py), 7.73 (γ, m, Py)].

METHOD S.1

Preparation of benzyl (17), 4-methylbenzyl (18), 4-isopropylbenzyl (19), 4-tert-butylbenzyl (20), 4-bromobenzyl (21), 4-chlorobenzyl (22), 4-cyanobenzyl (23), 4-formylbenzyl (24) 4-carboxybenzyl (25), 4-nitrobenzyl (26) cobaloximes

All the above (ten) compounds were prepared by the following general method:[37]

Cobalt(II) chloride hexahydrate (9.5 g, 40 mmol) and dimethylglyoxime (9.4 g, 80 mmol) were stirred in methanol (200 ml) in a 500 ml, three-neck RB flask fitted with a glass inlet tube, pressure equalising dropping funnel and an adapter outlet connected to a mercury trap. A stream of pure dry nitrogen was passed through the mixture for 30 minutes. An aqueous solution of sodium hydroxide (*ca*. 5-6 ml, 80 mmol) was added to the mixture followed by pyridine (2.2 ml, 40 mmol). The mixture was cooled in an ice bath (-10°C) and aqueous sodium hydroxide (*ca*. 3-4 ml, 40 mmol) was added followed by solid sodium borohydride (0.8 g, 20 mmol). A deep blue solution was formed. Appropriate organic halide (40 mmol) in methanol (10 ml) was added dropwise to the

reaction mixture. The colour changed from blue to orange red. The solution was stirred for another 3 hrs. and brought to ambient temperature. Approximately one-third volume of the solvent was evaporated under reduced pressure and the mixture was poured into water (200 ml) containing few drops of pyridine. The precipitated solid was washed with cold water (ca. 300 ml) until the washings were light pale yellow. It was then washed with ether (ca. 3 x 25 ml) and dried in vacuo. An analytical sample was obtained by recrystallizing the product from hot 5% ethanol, which was yellow to orange in colour.

METHOD S.2

Preparation of 4-acetamidobenzyl (27), 4-N,N-dimethylaminobenzyl (28), 4-methoxybenzyl (29), 3-methylbenzyl (30), 3-methoxybenzyl (31), methylene phenyl sulphide (32), methylene phenyl ether (33) cobaloximes

All the above (seven) cobaloximes were prepared by the following general method:[37]

Chloro(pyridine)cobaloxime(III) (16) (7.4 g, 20 mmol) was suspended, under nitrogen, in methanol (150 ml) in a 500 ml three neck flask. After stirring for fifteen minutes the reaction mixture was cooled to -10°C by ice-salt bath and a few drops of aqueous sodium hydroxide was added followed by solid sodium borohydride (0.4 g, 10 mmol).

To the resulting blue solution, an appropriate organic halide (20 ml) was added dropwise. The colour change from blue to orange red was slower in the case of tosylate than halide. After stirring at room temperature for additional time (2 hrs. for halide, 10 hrs. for tosylate) the methanolic solution was concentrated to one-third volume under vacuum and the mixture was poured into water, washed with ether and dried *in vacuo*. The crude product was purified by flash column chromatography using a mixture of dichloromethane, methanol, pyridine (90:9:1, v/v; *ca.* 200 ml) as eluent. The eluate was concentrated *in vacuo* and the residual crystals were pumped free of solvent at room temperature.

METHOD S.3

Preparation of bis(dimethylglyoximato)-C-methylene anilinato-pyridinatocobalt(III) (*34*)[71]

Dry methanol (400 ml) was placed into one litre three-necked flask and was thoroughly degassed with pure and dry nitrogen. Cobalt acetate (24.9 g, 10 mmol), dimethylglyoxime (23.2 g, 20 mmol) and pyridine (8.1 ml, 10 mmol) were added and the mixture was stirred under nitrogen for one hour. Nitrogen gas was replaced by stream of hydrogen and aniline (9.3 g, 10 mmol) and 40% formaldehyde solution (3.4 ml, 12 mmol) was added. After an hour, solution was doubled by addition of water and was allowed to stand overnight. The crystalline product

was collected, washed with ether and dried *in vacuo* (10.9 g, 44%).

METHOD S.4

Preparation of bis(dimethylglyoximato-borondifluoride)-4-methoxybenzyl pyridinatocobalt(III) (35)[292]

Pyridine was added slowly to a stirred suspension of 4-methoxybenzyl cobaloxime (29) and boron trifluoride etherate (10 ml) in diethyl ether (60 ml). After 48 hours of stirring the suspended solid was collected by filtration. Residue was washed with ether and dried *in vacuo*; yield (6.1 g, 70%). Recrystallization from acetone afforded ye llow crystals of the product (35).

^{1}H NMR (DMSO-d_6 + $CDCl_3$), δ (ppm): 2.54 (s, CH_3), 2.31 (s, CH_2), 6.89 (d, Ar), 7.26 (d, Ar), 8.9(α,d,Py), 8.58(β,m,Py), 8.13(γ, m,Py).

2.2.3 Reactions of Halogens with Organocobaloximes (17-34) in Chloroform and Acetic Acid

R.1 (a): A solution of halogen (1 or 2 mmol in 10 ml dry chloroform) was added dropwise into a solution of the organocobaloxime (1 mmol in 20 ml dry chloroform) in dark at room temperature under nitrogen atmosphere. The progress of the reaction which took 1-3 hours was monitored by tlc on silica gel using ethyl acetate as the eluent. On completion, the reaction

R.2 Reaction of 4-Nitrobenzyl cobaloxime (26) with Lithium Halide

A mixture of 4-nitrobenzyl cobaloxime (1.0 g, 2 mmol) and lithium chloride (1.7 g, 4 mmol) in chloroform (30 ml) was heated on a steam bath at 60°C. A slow stream of oxygen was bubbled through the mixture. After three hours, the mixture was poured on a silica gel column and eluted with dichloromethane. The organic product so obtained was further separated on the preparative silica gel plate by elution with pentane, dichloromethane (1:1) mixture. Inorganic product was eluted from the column using acetone as eluent.

R.3 Reaction of 4-Dimethylaminobenzyl cobaloxime (28) with Chlorine in the presence of Thiophenol and Triethylamine

Chlorine (2 mmol in 10 ml dry chloroform) was added dropwise over a period of twenty minutes to a solution of 4-dimethylaminobenzyl cobaloxime (1 mmol in 15 ml chloroform) in dark under nitrogen and in the presence of thiophenol and triethylamine (both 1 mmol each). The progress of the reaction which took less than 45 minutes was monitored by tlc on silica gel using ethyl acetate as eluent.

Reaction mixture was concentrated *in vacuo* and poured on neutral alumina column for flash column chromatography. Organic product was eluted with ether solvent. The ether layer

was dried over sodium sulphate and evaporated under reduced pressure. Organic compound so obtained was subjected to spectral analysis. Inorganic product was eluted from the column using dichloromethane and was further purified on preparative alumina (neutral) plate using ethyl acetate as eluent.

R.4 Reaction of 4-Nitrobenzyl cobaloxime (26) with Chlorine in the presence of one equivalent of Tetramethylammonium Bromide in Acetic Acid

Chlorine (1 mmol in 10 ml acetic acid) was added dropwise to a solution of 4-nitrobenzyl cobaloxime (1 mmol in 15 ml acetic acid) in the presence of 1 mmol tetramethylammonium bromide in dark under nitrogen. Reaction procedure was followed as that of R.1(b).

R.5 Reaction of 4-Nitrobenzyl cobaloxime (26) with Bromine in the presence of one equivalent of Tetramethylammonium Chloride in Acetic Acid

Reaction of 4-nitrobenzyl cobaloxime with bromine in the presence of one equivalent of tetramethylammonium chloride in acetic acid was carried out following a procedure as that of R.1(b).

R.6 Reaction of 4-Nitrobenzyl cobaloxime (26) with chlorine in the presence of excess Tetramethylammonium Bromide in Acetic Acid

Reaction of 4-nitrobenzyl cobaloxime with chlorine in the presence of tetramethylammonium bromide (excess) was carried out following a procedure as that of R.1(b).

R.7 Reaction of 4-Methylbenzyl cobaloxime (18) with Bromine in the presence of 20% Sulphuric Acid

Sulphuric acid (20%) was added to 4-methylbenzyl cobaloxime (0.9 g, 2 mmol in 15 ml chloroform). Bromine (0.6 g, 4 mmol) was added dropwise to the above solution in dark and under nitrogen. The progress of reaction was monitored by tlc on silica gel using ethyl acetate as eluent. On completion (1.5 hrs.), the mixture was poured into ether ($\simeq$ 50 ml). The precipitated inorganic product was filtered off and washed with solvent ether. The filtrate and the combined ether extracts were washed successively with sodium bicarbonate, sodium meta-bisulphite and water. The organic layer was dried over magnesium-sulphate and evaporated to afford the organic product.

R.8 Reaction of bis(dimethylglyoximato-borondifluoride) 4-methoxybenzyl pyridinatocobalt(III) (35) with Bromine

Bis(dimethylglyoximato-borondifluoride) 4-methoxybenzyl-pyridinatocobalt(III) (35) (0.5 g, 1 mmol in 15 ml glacial

acetic acid) was treated with bromine (0.3 g, 2 mmol in 10 ml glacial acetic acid) dropwise under nitrogen in dark. The progress of the reaction was monitored by tlc on silica gel using ethyl acetate:methanol (95:5) mixture as eluent. On completion (1 hr) the reaction mixture was poured into ether (100 ml). The precipita ed inorganic product was filtered and washed with ether. Filtrate and washings were combined and evaporated in vacuo to obtain organic product, which was characterized by glc and ^{1}H NMR.

R.9 Reaction of 4-Methoxybenzyl cobaloxime (29) with Hydrogen Bromide

Hydrogen bromide gas generated by equimolar reaction of tetralin with dry bromine was solvated in dry chloroform. HBr solution (0.2 g, 2 mmol) in chloroform (10 ml) was added dropwise to a solution of 4-methoxybenzyl cobaloxime (29) (0.5 g, 1 mmol) in chloroform (15 ml) under nitrogen in dark.

The progress of reaction was monitored by tlc on silica gel using ethyl acetate as eluent. No change in starting material occurred even after four hours which was the stipulated time for the reaction type R.1. No reaction took place even on prolonged standing (72 hours) and only the starting organocobaloxime was recovered back.

R.10 Reaction of Organometallic Products (80-85) with Excess Halogen Photolytically

Organometallic products obtained from different reactions were further halogenated by excess halogen in the presence of 2 x 200 W tungsten lamps. This was done to ascertain the proper position of the halogen in the ring. Reaction was, in general, carried out at 0.5 g scale of organometallic product with atleast four-fold excess of halogen in dry chloroform (10 ml) under nitrogen.

Reaction mixture was stirred at room temperature upto the completion of reaction which was checked by silica gel tlc. After that, reaction mixture was poured over 5 inch fluorocil column to remove inorganic product. Organic product was eluted with ether. Organic product was characterized by ^{1}H NMR and mass spectroscopy.

R.11 Reaction of C-Bonded Phenyl methylene ether $Co^{III}(dmgH)_2Py$ (33) with Bromine (1:1 molar ratio) in the presence of Equimolar Ratio of Anisole

Bromine (1 mmol in 10 ml dry chloroform) was added dropwise over a period of 20 minutes to a solution of (33) (1 mmol in 15 ml dry chloroform) in dark, under nitrogen, in the presence of anisole (1 mmol). The progress of the reaction which took less than 45 minutes was monitored by tlc on silica gel using ethyl acetate as eluent.

Reaction mixture was concentrated *in vacuo* and poured on a neutral alumina column for flash chromatography. Organic product was eluted with ether-solvent and the inorganic part with dichloromethane. Respective solvents were dried and evaporated. The productsthus obtained were characterized using conventional analytical methods.

2.3 Results

2.3.1 Formation of Organocobaloximes (17-34)

Benzyl and substituted benzyl cobaloximes (17-31), methylene phenyl sulphide (32) and methylene phenyl ether (33) cobaloximes are synthesized by reacting the appropriate halide or tosylate with preformed (Co^{I}), the latter being generated either by the reaction of ($Cl\text{-}Co^{III}$) with sodium borohydride in neutral or slightly alkaline medium[292] or by the disproportionation of (Co^{II}) into (Co^{III}) and (Co^{I}) in highly alkaline medium.[85,293-299]

The reactions of (Co^{I}) with halides are visibly faster as compared to the reaction with tosylate (only on the the basis of colour change from blue (Co^{I}) to red (Co^{III})). This is justified since compared to halide, tosyl group is hard leaving group and S_N2 reaction with the soft and bulky nucleophilic, (Co^{I}) will be sluggish. The organocobaloximes have been isolated by standard workups in all cases[292] except for

4- and 3-methoxybenzyl cobaloximes (29, 31), 4-N,N-dimethylaminobenzyl cobaloxime (28) and methylene phenyl ether cobaloximes (33). All these cobaloximes are found to be rather unstable in air in aqueous solution, probably due to the tendency for the axial pyridine ligand to come off; rendering a five coordinated species that goes into water during workup procedure. These cobaloximes, therefore, are isolated under nitrogen atmosphere followed by flash column chromatography using acetone as eluent.[95] Although the free radical and electron transfer mechanism have recently been described in literature,[39,55-58,300-303] the mechanism for the formation of cobaloximes in our case follows a S_N2 displacement of the halide/tosylate ion by (Co^I) nucleophile. This latter mechanism is well supported by literature,[41,42] for example, benzylation of (Co^I) nucleophile with benzyl halide is an established S_N2 mechanism.[50]

C-Bonded methylene anilinatocobaloxime (34) is synthesized by reacting hydrido(pyridine)cobaloxime with aniline in the presence of formaldehyde.[71,304] The mechanism of the reaction is intriguing and has not been studied fully. However, it seems possible that the reaction represents attack of the hydrido species on the Schiff base (or carbinolamine) formed in situ from aniline and formaldehyde.

The spectral characteristics of the cobaloximes are listed in Table 2.1.

Table 2.1: Spectral Characteristic of Organocobaloximes $RCo^{III}(dmgH)_2Py$ (16-34)*

Sl. No.	Compound No.	R	^1H NMR Chemical Shift (δ): ($CDCl_3$) (ppm), (TMS)							UV-vis: λ_{max} (nm) (CH_3OH)
			dmgH	CH_2	Aromatic	Pyridine β	Pyridine γ	Pyridine α	Others	
1	2	3	4	5	6	7	8	0	10	11
0.	(16)	Cl	2.35	-	-	7.26	7.73	8.25	-	468, 360, 275, 233
1.	(17)	$C_6H_5CH_2$	1.90	2.80	6.95	7.32	7.73	8.40	-	455, 352, 272, 238
2.	(18)	4-$MeC_6H_4CH_2$	1.95	2.90	6.90	7.36	7.78	8.52	2.08 (Me)	452, 356, 274, 237
3.	(19)	4-$Me_2CHC_6H_4CH_2$	1.95	2.85	6.85	7.20	7.60	8.45	1.20 (Me), 2.55-3.20(-CH)	452, 364, 273, 235
4.	(20)	4-$Me_3CC_6H_4CH_2$	1.95	2.85	7.08-7.15	7.25	7.70	8.55	1.25 (Me)	450, 360, 276, 233
5.	(21)	4-$BrC_6H_4CH_2$	1.98	2.82	7.00-7.45	7.40	7.90	8.56	-	421, 347, 262, 227
6.	(22)	4-$ClC_6H_4CH_2$	2.00	2.73	7.20	7.30	7.80	8.56	-	455, 353, 270, 240
7.	(23)	4-$CNC_6H_4CH_2$	1.98	2.71	6.90-7.30	7.25	7.70	8.50	-	460, 340, 277, 237
8.	(24)	4-$CHOC_6H_4CH_2$	1.96	2.78	6.98-7.40	7.30	7.65	8.52	9.86 (CHO)	458, 342, 277, 238

...contd.

Table 2.1 (contd.)

1	2	3	4	5	6	7	8	9	10	11
9.	(25)	4-$COOHC_6H_4CH_2$	1.98	2.82	6.96-7.40	7.33	7.62	8.48	9.90 (OH)	448, 342, 275, 233
10.	(26)	4-$NO_2C_6H_4CH_2$	2.06	3.35	6.86-7.54	7.72	8.22	8.76	-	445, 350, 300, 235
11.	(27)	4-$NHCOCH_3$-$C_6H_4CH_2$	1.93	2.82	6.80-7.22	7.28	7.65	8.55	2.10 (Me)	450, 365, 285, 235
12.	(28)	4-$NMe_2C_6H_4CH_2$	2.03	2.85	6.50-7.10	7.20	7.55	8.34	2.92 (Me)	428, 352, 313, 245
13.	(29)	4-$MeOC_6H_4CH_2$	1.95	2.85	6.60-6.90	7.25	7.68	8.55	3.75 (OMe)	448, 380, 287, 232
14.	(30)	3-$MeC_6H_4CH_2$	1.95	2.85	6.70-7.20	7.36	7.78	8.44	2.30 (Me)	454, 358, 270, 235
15.	(31)	3-$MeOC_6H_4CH_2$	2.10	2.90	6.50-7.00	7.20	7.60	8.44	3.88 (OMe)	457, 352, 270, 232
16.	(32)	$C_6H_5SCH_2$	2.00	3.10	6.98-7.63	7.74	8.10	8.52	-	435, 385, 287, 232
17.	(33)	$C_6H_5OCH_2$	1.90	4.80	6.60-7.42	7.54	7.98	8.53	-	427, 327, 250, 230
18.	(34)	$C_6H_5NHCH_2$	1.85	5.15	6.30-7.35	7.82	8.06	8.60	4.65 (NH)	450, 308, 272, 240

*All compounds give satisfactory C, H, N analyses.

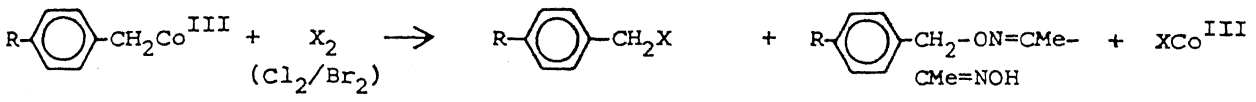
2.3.2 Reaction of Benzyl (17) and Substituted Benzylcobaloximes (18-31) with Halogens

Benzyl cobaloxime (17) reacts with 1:1 or 1:2 molar equivalents of halogens (Cl_2 or Br_2) in chloroform or acetic acid in dark at room temperature and under nitrogen atmosphere. The reactions are done under conditions where the concentration of halogen is kept very low and the reactions of higher order in halogen are negligible. Within the reaction time the benzyl cobaloxime (17) does not show any sign of decomposition in absence of halogen. A smooth reaction takes place and is complete in 2 hours. Benzyl bromide (38) is the sole organic product formed in bromination, however, benzyl chloride (39) and benzyl ether of dimethylgloxime (71) (62:38 ratio) are formed in chlorination. The inorganic product being the corresponding halocobaloxime (36 or 16).

Similar reactions of substituted benzyl cobaloximes (18-26) with halogens (Cl_2 or Br_2) under identical reaction conditions form benzyl halides (40-57) and benzyl ethers of dimethylglyoximes (71-77) in varying proportions (Scheme 2.2, Table 2.2.A) along with halocobaloxime.

All the organic halides so formed are known in literature and are, therefore, identified by the ^1H NMR spectra and by comparison with authentic samples wherever possible. The product ratios are based on the ^1H NMR spectra and GLC. Benzyl ethers of dimethylglyoximes (71-77) are characterized by ^1H NMR

Scheme 2.2: Products of Reaction of Halogens with Benzyl cobaloximes (17-26) in Chloroform or Acetic Acid

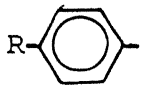


(17) R = H
(18) R = Me
(19) R = Me_2CH
(20) R = Me_3C
(21) R = Br
(22) R = Cl
(23) R = CN
(24) R = CHO
(25) R = COOH
(26) R = NO_2

(38) R = H; X = Br
(39) R = H; X = Cl
(40) R = Me; X = Br
(41) R = Me; X = Cl
(42) R = Me_2CH; X = Br
(43) R = Me_2CH; X = Cl
(44) R = Me_3C; X = Br
(45) R = Me_3C; X = Cl
(46) R = Br; X = Br
(47) R = Br; X = Cl
(48) R = Cl; X = Br
(49) R = Cl; X = Cl
(50) R = CN; X = Br
(51) R = CN; X = Cl
(52) R = CHO; X = Br
(53) R = CHO; X = Cl
(54) R = COOH; X = Br
(55) R = COOH; X = Cl
(56) R = NO_2; X = Br
(57) R = NO_2; X = Cl

(71) R = H
(72) R = Br
(73) R = Cl
(74) R = CN
(75) R = CHO
(76) R = COOH
(77) R = NO_2

(16) X = Cl
(36) X = Br

Table 2.2.A: Organic Products from the Reaction of  (17-26) with Halogens in Acetic Acid

Cobaloxime (1 mol)	Halogen (2 mol)	Organic Product (product number)	Yield (%)[a]
(17)	Br_2	$BrCH_2C_6H_5$ (38)	(⩾90)[b]
(17)	Cl_2	$ClCH_2C_6H_5$ (39)	(62)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_5$ (71)	(38)
(18)	Br_2	$BrCH_2C_6H_4Me$-4 (40)	(⩾90)
(18)	Cl_2	$ClCH_2C_6H_4Me$-4 (41)	(⩾95)
(19)	Br_2	$BrCH_2C_6H_4CH(Me)_2$-4 (42)	(⩾92)
(19)	Cl_2	$ClCH_2C_6H_4CH(Me)_2$-4 (43)	(⩾95)
(20)	Br_2	$BrCH_2C_6H_4C(Me)_3$-4 (44)	(⩾95)
(20)	Cl_2	$ClCH_2C_6H_4C(Me)_3$-4 (45)	(⩾95)
(21)	Br_2	$BrCH_2C_6H_4Br$-4 (46)	(⩾90)
(21)	Cl_2	$ClCH_2C_6H_4Br$-4 (47)	(72)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4Br$-4 (72)	(28)
(22)	Br_2	$BrCH_2C_6H_4Cl$-4 (48)	(92)
(22)	Cl_2	$ClCH_2C_6H_4Cl$-4 (49)	(65)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4Cl$-4 (73)	(35)
(23)	Br_2	$BrCH_2C_6H_4CN$-4 (50)	(90)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4CN$-4 (74)	(10)
(23)	Cl_2	$ClCH_2C_6H_4CN$-4 (51)	(64)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4CN$-4 (74)	(36)
(24)	Br_2	$BrCH_2C_6H_4CHO$-4 (52)	(90)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4CHO$-4 (75)	(10)

....contd..

Table 2.2.A (contd.)

Cobaloxime (1 mol)	Halogen (2 mol)	Organic Product (product number)	Yield (%)[a]
(24)	Cl_2	$ClCH_2C_6H_4CHO$-4 (53)	(62)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4CHO$-4 (75)	(38)
(25)	Br_2	$BrCH_2C_6H_4COOH$-4 (54)	(90)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4COOH$-4 (76)	(10)
(25)	Cl_2	$ClCH_2C_6H_4COOH$-4 (55)	(63)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4COOH$-4 (76)	(35)
(26)	Br_2	$BrCH_2C_6H_4NO_2$-4 (56)	(80)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4NO_2$-4 (77)	(20)
(26)	Cl_2	$ClCH_2C_6H_4NO_2$-4 (57)	(55)
		$NOH{=}CMe{-}CMe{=}NOCH_2C_6H_4NO_2$-4 (77)	(40)

a) Based on ^1H NMR and GLC

b) From ref. 299.

Table 2.2.B: Characteristics of Benzyl ethers of Dimethylglyoxime (71-77)

Compound No.	M.P. (°C)	^{1}H NMR: δ ($CDCl_3$), TMS			Mass[d]: m/e (%)	UV: λ_{max} (nm) (CH_3OH)
		Aromatic	$-CH_2$	dmgH		
(71)[a]	90-92	7.23	5.10	2.00	-	-
(72)[b]	100	A. 7.12, 7.32	5.14	1.90, 2.30	285(2%), 170(100%)	220
		B. 7.12, 7.32	5.10	2.22, 2.35	283(2%), 168(100%)	
(73)	98	7.20	5.16	1.90, 2.30	239(1.5%), 124(100%)	226
(74)	95	7.40, 7.52	5.16	1.95, 2.04	231(10%), 116(100%)	235
(75)[c]	93	7.52, 7.90	5.18	2.25, 2.28	234(6%), 119(98%)	236, 273
(76)	e	7.48, 7.82	5.18	2.20, 2.26	250(8%), 135(94%)	230, 282
(77)[b]	99	A. 7.50, 8.20	5.35	2.05, 2.35	250(60%), 135(100%)	217, 230
		B. 7.50, 8.20	5.10	2.18, 2.22	250(62%), 135(100%)	

a) From ref. 299; b) Both isomers (syn and anti) are observed in ^{1}H NMR; C) CHO appears at 10.0δ; d) First value corresponds to M^+ and second value to $R\text{-}C_6H_4CH_2^+$ species; e) More than 200°C.

and mass spectroscopy and their detailed characteristics are given in Table 2.2.B.

Unlike the above cases, the reaction of benzyl cobaloximes (27-31) with halogens form entirely different products, for example, 4-acetamidobenzyl cobaloxime (27) with Br_2 in 1:1 molar ratio forms both organic (58) and organometallic product (80) in 44:56 ratio. The same reaction with 1 mol excess of bromine forms an additional organic product (59) which results due to the cleavage of Co-C bond in (80). Similarly, the reaction of (27) with Cl_2 forms both organic and organometallic product in varying amounts (Scheme 2.3). A small amount ($\simeq$ 5%) of 4-acetamidobenzyl ether of dimethylglyoxime (78) is also isolated (m.p. 85°C); ^{1}H NMR ($CDCl_3$), δ (ppm): 7.12-7.73 (m, Ph), 5.18 (s, CH_2), 2.08, 2.22 (s, dmgH), 2.12 (s, $NHCOCH_3$), 2.76 (br, NH), 8.12 (br, NOH); m/e: 263; UV (CH_3OH): 285.5, 231 nm.

4-N,N-Dimethylaminobenzyl cobaloxime (28) with bromine (1 or 2 equivalents) forms only the ring substituted organometallic product (82) whereas chlorination gives both organic and organometallic products. The organic product, 4-N,N-dimethylaminobenzyl chloride so formed is highly unstable and is, therefore, isolated and characterised as (62) by its reaction with thiophenol/Et_3N (Scheme 2.3).

Interestingly, the halogenation of 4-methoxybenzyl cobaloxime (29) with Br_2 and Cl_2 forms exclusively 4-methoxy-2-halotoluene (63 and 64) in quantitative yield (Scheme 2.3).

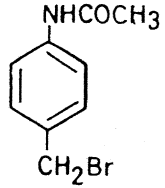
Scheme 2.3: Products of the Reaction of Benzyl cobaloximes (27-31) with Halogens in Chloroform

$RCo^{III}(dmgH)_2Py$	X_2 (mol)	Products[a]	%age ratio[b]
R = 4-Acetamido benzyl (27)	Br_2 (1)	(58), (80)	44, 56
	Br_2 (2)	(58), (59), (80)	48, 17, 35
	Cl_2 (1)	(60), (61), (81)	55, 15, 30
	Cl_2 (2)	(60), (61), (81)	57, 18, 25
R = 4-N,N-dimethyl benzyl (28)	Br_2 (1 or 2)	(82)	100
	Cl_2 (1)	(62), (83)	33, 67
	Cl_2 (2)	(62), (83)	40, 60
R = 4-Methoxy benzyl (29)	Br_2 (1 or 2)	(63)	100
	Cl_2 (1 or 2)	(64)	100
R = 3-Methyl benzyl (30)	Br_2 (2)	(65), (66)	50, 50
	Cl_2 (2)	(67), (68)	75, 25
R = 2-Methyl benzyl	Br_2 (1)	(69), (84)	42, 56
	Br_2 (2)	(69), (84)	60, 40
	Cl_2 (1)	(70), (85)	46, 51
	Cl_2 (2)	(70), (85)	69, 35

a) See next page for product numbers;

b) Product ratio based on isolated yield (isolation >90% in all cases).

Scheme 2.3 (contd.) Product numbers with structure.



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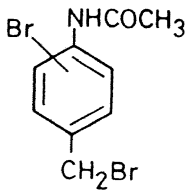

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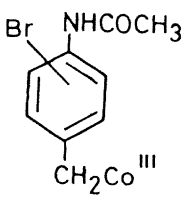

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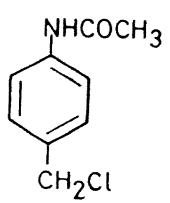

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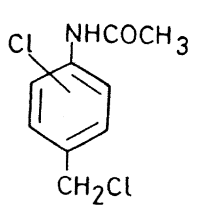

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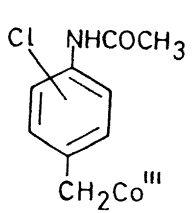

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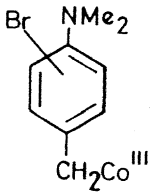

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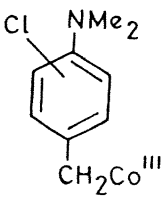

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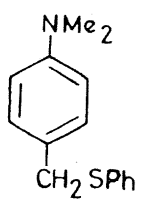

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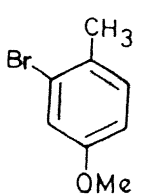

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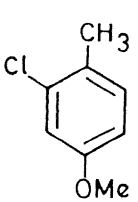

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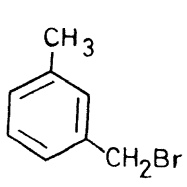

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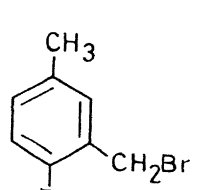

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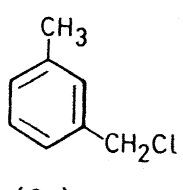

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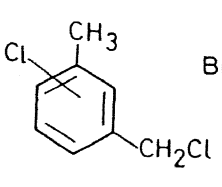

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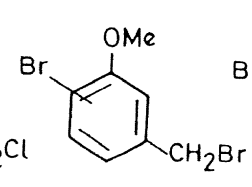

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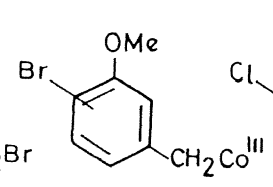

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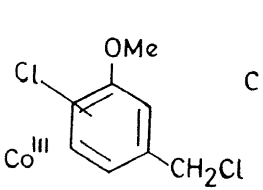

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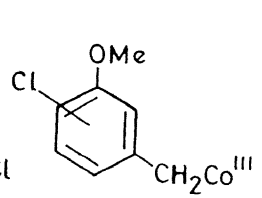

(85)*

* mixture of twopositional isomers

3-Methylbenzyl cobaloxime (30) with Br_2 under similar conditions forms 3-methylbenzyl bromide (65) and 3-methyl-6-bromobenzyl bromide (66) in 50:50 ratio whereas chlorination of (30) gives 3-methylbenzyl chloride (67) and 3-methyl-X-chlorobenzyl chloride (68) in 75:25 ratio. The assignment of the position of chlorine in the ring in (68) is not clear due to the compact nature of aromatic proton resonances. However, ^1H NMR spectrum of (68) points it to be a mixture of two positional isomers. The inorganic product in these reactions is the corresponding halocobaloxime.

On the other hand, reaction of 3-methoxybenzyl cobaloxime (31) with halogen (Br_2 or Cl_2) (1 or 2 equivalents) forms both organic (69), (70) and organometallic product (84), (85) in varying proportions (Scheme 2.3). Each of these products is a mixture of two positional isomers as shown by ^1H NMR. All efforts to separate these mixture on chromatography fail since the r.f. values are very close to each other (many solvent systems tried).* Spectral and analytical characteristics of the organic (50-70) and organometallic products (80-85) are shown in Tables 2.3.A and 2.3.B, respectively (pp. 112 & 114).

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*Separation of isomers by glc (SE-30 column) led to the decomposition of organic products. Similarly, both isomers could not be separated by HPLC also.

Table 2.3.A: Spectral and Analytical Characteristics of the Organic Products (50-70) from the Reaction of Halogens with Benzyl cobaloximes (27-31)

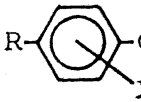
Compound No.	m.p./b.p.* (°C)	^{1}H NMR Chemical Shift, (δ) (ppm): $CDCl_3$			UV: λ_{max} (nm) (CH_3OH)
		Aromatic	CH_2	Others	
1	2	3	4	5	6
(58)	186	7.00-7.44(m)	4.34(s)	2.05(s) (Me)	285, 239
(59)	210	8.06-8.30(m)	4.47(s)	2.23(s) (Me)	284, 234
(60)	151-153	7.18-7.56(m)	4.53(s)	2.16(s) (Me)	289, 227
(61)	182-183	7.96-8.20(m)	4.40(s)	2.12(s) (Me)	286, 238
(62)	57	7.00-7.80(m)	3.80(s)	2.88(s) (Me)	313, 302, 256
(63)	110-113/8 mm*	6.75-7.40(m)	-	2.26 (Me), 3.80 (OMe)	216, 245, 287, 310(sh)
(64)	88/5 mm*	6.80-7.50(m)	-	2.34 (Me), 3.91 (OMe)	216, 249, 282, 301(sh)
(65)	74/10 mm*	7.08(m)	4.38(s)	2.24 (Me)	270, 235
(66)	81/5 mm*	7.10(m)	4.45(s)	2.29 (Me)	274, 235

....contd.

Table 2.3.A (contd.)

1	2	3	4	5	6
(67)	82/10 mm*	7.14 (m)	4.44(s)	2.36 (Me)	268, 232
(68)	94/5 mm*	7.14(m)	4.47(m)	2.36 (Me)	268, 231
(69)‡	91-98	6.60-7.58(m)	4.50(s), 4.55(s)	(3.90, 3.80) (OMe)	213, 239, 293 304(sh)
(70)‡	39-45	6.53-7.42(m)	4.40, 4.46	(3.86, 3.80) (OMe)	212, 229, 287, 279, 309(sh)

‡Positional isomers.

Table 2.3.B: Spectral and Analytical Characteristics of R-  -$CH_2Co^{III}(dmgH)_2Py$ (80-85)

R	X	^{1}H NMR Chemical Shift (δ): ($CDCl_3$) (ppm)							Analysis: Found (Calcd), %				UV-v
		dmgH	Aromatic	CH_2	Pyridine β	Pyridine γ	Pyridine α	Others	C	H	N	X	λ_{max} (CH
4-NHCOMe (80)	Br	2.05	7.23-7.90	3.09	7.60	7.76	8.43	2.30[a]	44.2 (44.3)	4.87 (4.7)	14.6 (14.1)	13.4 (13.4)	456, 280,
4-NHCOMe (81)	Cl	2.15	7.00-7.50	2.99	7.54	7.74	8.60	2.23[a]	47.5 (47.9)	4.82 (5.0)	15.0 (15.2)	6.3 (6.4)	460, 282,
4-N(Me)$_2$ (82)	Br	2.10	7.00-7.55	2.78	7.70	7.78	8.50	2.88[b]	45.6 (45.3)	5.3 (5.1)	14.5 (14.4)	13.9 (13.7)	435, 323,
4-N(Me)$_2$ (83)	Cl	2.06	7.00-7.36	2.77	7.40	7.60	8.44	2.84[b]	49.3 (49.1)	5.7 (5.5)	15.8 (15.8)	6.6 (6.6)	432, 320,
3-OMe* (84)	Br	2.02	6.34-7.40	2.88	7.30	7.70	8.54	3.88[c]	44.6 (44.3)	4.87 (4.7)	12.3 (12.8)	14.2 (14.0)	469, 277,
		1.98	6.34-7.40	2.75	7.30	7.70	8.84	3.77[c]					
3-OMe* (85)	Cl	2.10	6.28-6.90	2.80	7.40	7.77	8.48	3.92[c]	48.0 (48.1)	5.28 (5.1)	13.4 (13.7)	6.8 (6.7)	466, 279,
		2.00	6.28-6.90	2.72	7.40	7.77	8.48	3.86[c]					

*having positional isomers.

a) -NHCOMe; b) -NMe_2; c) -OCH_3

Many independent experiments give the following information:

(i) Chlorination of 4-nitrobenzyl cobaloxime (26) in acetic acid in the presence of 1 mol of bromine ion added as $[(CH_3)_4NBr]$ gives a mixture of 4-nitrobenzyl bromide (56) and 4-nitrobenzyl chloride (57). The comparative yield of 4-nitrobenzyl bromide is greater than the corresponding chloride when the same reaction is done in the presence of large excess of bromide ion. The extent of the formation of 4-nitrobenzyl ether of dimethylglyoxime (77) gets lowered, however.

(ii) Bromination of 4-nitrobenzyl cobaloxime (26) in acetic acid in the presence of large excess of chloride ion (added as $(CH_3)_4NCl$) forms a mixture of 4-nitrobenzyl chloride (57) and 4-nitrobenzyl bromide (56). However, the extent of the formation of ether product (77) is higher in this case as compared to the corresponding reaction described above under case (i).

(iii) The reaction of 4-nitrobenzyl cobaloxime (26) with lithium halide in chloroform at 60°C with constant bubbling of oxygen into the solution gives a mixture of 4-nitrobenzyl halide (56,57) and 4-nitrobenzyl ether of dimethylglyoxime (77).

(iv) Reaction of 4-methylbenzyl cobaloxime (18) with bromine forms exclusively 4-methylbenzyl bromide (40) whereas the bromination of (18) in the presence of 20% sulphuric acid

forms a mixture of 4-methylbenzyl bromide (40) and 4-methylbenzyl ether of dimethylglyoxime (79)* in 10:90 ratio. However, the bromination of monoprotonated 4-methylbenzyl cobaloxime (37) (protonated by 20% sulphuric acid and then isolated and purified) forms (40) and (79) in 30:70 ratio.

(v) 4-Methoxybenzyl cobaloxime (29) does not show any sign of reaction with pure HBr in chloroform under nitrogen even after 72 hours. The original cobaloxime is recovered back.

(vi) The reaction of 4-methoxybenzyl cobaloxime (29) in the presence or absence of K_2CO_3 forms the same product, 4-methoxy-2-halo toluene.

(vii) In the reaction of 3-methoxybenzyl cobaloxime (31) with bromine, a careful monitoring of the reaction indicates that the organic product is formed simultaneously with the organometallic product right from the very beginning and its formation is not a later phenomenon.

(viii) The reaction of $4\text{-OMeC}_6H_4CH_2Co(dmgBF_2)_2Py$ (35) with bromine forms $4\text{-OMeC}_6H_4CH_2Br$ and $HON{=}CMe\text{-}CMe{=}NOCH_2C_6H_4OMe\text{-}4$ in a ratio of 80:20 (from ^1H NMR only). However, the reaction time is much longer as compared to the reaction of 29 with Br_2.

(ix) Chlorinations, in general are more rapid than brominations.

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*(79): (m.p. 85°C); ^1H NMR ($CDCl_3$), δ (ppm): 7.16 (m, Ph), 5.12 (s, CH_2), 2.00, 2.08 (s, (dmgH); m/e: 220; UV (CH_3OH), λ(nm): 228.

(x) No appreciable change in reaction time is noted when the solvent is changed from chloroform to acetic acid. Same products are formed in both cases, however, the yields are slightly better ($\backsim$10%) in chloroform reaction.

(xi) In the reaction of (27) with halogens (Br_2 and Cl_2) all efforts to separate the product mixtures (58 and 59) and (60 and 61) by chromatography fail (many solvent systems are tried) and hence the position of halogen in the ring cannot be accurately assigned. Similarly, the position of halogen in the organometallic products (80), (81), (82) and (83) cannot be accurately assigned because of the complexities of the aromatic region and also because part of the aromatic region is obscured by pyridine resonances. Furthermore, the reaction of organometallic products (80-83) with halogen, under photolytic conditions, though exclusively cleaves Co-C bond, does not help in the assignment of halogen into the ring.

2.3.3 Reaction of C-Bonded Methylene-Y-Phenylcobaloxime (32-34) (Y = S, O, NH) with Halogens and Interhalogen

Cobaloximes (32-34) react with 1:1 or 1:2 molar equivalents of halogens (Cl_2, Br_2, I_2 and ICI) in chloroform in the dark at room temperature and under nitrogen atmosphere. Once

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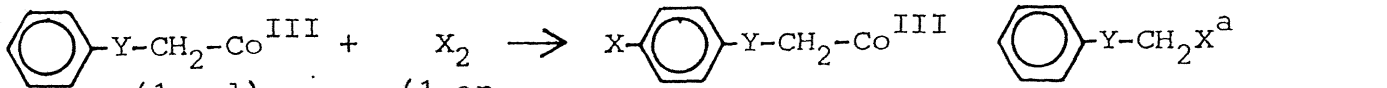
*A mixture of (58 and 59) when put on glc (SE-30 column) for analysis, decomposes.

again, all the reactions are carried out under conditions where the concentration of the halogen is kept as low as possible so that the reactions of higher order in halogen are negligible. A smooth reaction takes place and is complete within one hour (Cl_2 and Br_2) and in four hours (I_2 and ICl). Within the reaction time scale the cobaloximes do not show any sign of decomposition in absence of halogen.

The ring substituted organometallic products (86-94) are the main products isolated in each case. Besides, some organic products (95-103) are formed and characterized by their ^1H NMR spectra and by comparison with authentic samples in some cases. The inorganic product being the corresponding halocobaloxime (16, 36, 104; Scheme 2.4; Table 2.4.A). In cobaloximes (32, 33) the selectivity of attack of bromine on the ring is better maintained. In case of reactions with I_2 and ICl an additional small amount of O-organodimethylglyoxime mono ether (105-107) is isolated and characterised.

In case of the reaction of organocobaloxime (33) with bromine (1:2 molar ratio), the monitoring of the reaction by taking aliquots at regular intervals of 15 minutes indicates the simultaneous formation of (90) and (99), respectively. When the reaction of (32-34) with 2 moles of bromine is left for longer time (12-15 hours) at room temperature (108-110) are the main products characterised instead of (87, 90, 93). Reaction of organocobaloxime (33) with bromine (1:1 molar ratio) in

Scheme 2.4: Products of Reaction of Halogens (X_2) with Organocobaloxime (32-34) in chlorofo.



1	2	3	4	5
Y = S (32)	Cl_2	Y = S; X = Cl (86)	Y = S; X = Cl (95)	
Y = S (32)	Br_2	Y = S; X = Br (87)	Y = S; X = Br (96)	
Y = S (32)	Br_2(2)[d]		Y = S; X = Br (96)	Y = S; X = Br (108)
Y = S (32)	I_2[c]	Y = S; X = I (88)	Y = S; X = I (97)	
Y = S (32)	ICl[c]	Y = S; X = I (88)	Y = S; X = I (97)	
			Y = S; X = Cl (95)	
Y = O (33)	Cl_2	Y = O; X = Cl (89)	Y = O; X = Cl (98)	
Y = O (33)	Br_2	Y = O; X = Br (90)	Y = O; X = Br (99)	
Y = O (33)	Br_2(2)[d]		Y = O; X = Br (99)	Y = S; X = Br (109)
Y = O (33)	I_2[c]	Y = O; X = I (91)	Y = O; X = I (100)	
Y = O (33)	ICl[c]	Y = O; X = I (91)	Y = O; X = I (100)	
			Y = O; X = Cl (98)	

...contd.

Scheme 2.4 (contd.)

1	2	3	4	5
Y = NH (34)	Cl_2	Y = NH; X = Cl (92)	Y = NH; X = Cl (101)	
Y = NH (34)	Br_2	Y = NH; X = Br (93)	Y = NH; X = Br (102)	
Y = NH (34)	Br_2 (2)[d]		Y = NH; X = Br (102)	Y = NH; X = Br (110)
Y = NH (34)	I_2[c]	Y = NH; X = I (94)	Y = NH; X = I (103)	
Y = NH (34)	ICl[c]	Y = NH; X = I (94)	Y = NH; X = I (103)	
			Y = NH; X = Cl (101)	

Co^{III} = $Co^{III}(dmgH)_2Py$

a, b) Compounds are characterised mostly by ^1H NMR spectroscopy and by comparison with authentic samples in some cases; c) in these reactions 5-10% of $HON{=}CMe{-}CMe{=}NOCH_2YPh$ (105-107) is also obtained; d) left for longer time (12-15 hrs.); e) inorganic products are chloro (16), bromo (36) and iodo (104) cobaloximes.

Table 2.4.A: Products from the Reaction of Ph-Y-CH_2-Co^{III} (32-34) with Halogen in Chloroform

Substrate (1 mol)	Halogen (1 or 2 mol)	Product (product number)	Isolated Yield (%)
1	2	3	4
(32)	Cl_2	4-Cl $C_6H_4SCH_2Co^{III}$ (86)	69
		$C_6H_5SCH_2Cl$ (95)	30
(32)	Br_2	4-$BrC_6H_4SCH_2Co^{III}$ (87)	57
		$C_6H_5SCH_2Br$ (96)	43
(32)	Br_2 (2)*	4-$BrC_6H_4SCH_2Br$ (108)	53
		$C_6H_5SCH_2Br$ (96)	43
(32)	I_2	4-$IC_6H_4SCH_2Co^{III}$ (88)	85
		$C_6H_5SCH_2I$ (97)	10
		$C_6H_5SCH_2$-ON=C(Me)-C(Me)=NOH (105)	5
(32)	ICl	4-$IC_6H_4SCH_2Co^{III}$ (88)	55
		$C_6H_5SCH_2I$ (97) + $C_6H_5SCH_2Cl$ (95)	37
		$C_6H_5SCH_2$-ON=C(Me)-C(Me)=NOH (105)	8

Table 2.4.A (contd.)

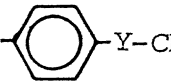
1	2	3	4
(33)	Cl_2	$4\text{-}ClC_6H_4OCH_2Co^{III}$ (89)	88
		$C_6H_5OCH_2Cl$ (98)	12
(33)	Br_2	$4\text{-}BrC_6H_4OCH_2Co^{III}$ (90)	54
		$C_6H_5OCH_2Br$ (99)	42
(33)	Br_2 (2)*	$4\text{-}BrC_6H_4OCH_2Br$ (109)	56
		$C_6H_5OCH_2Br$ (99)	42
(33)	I_2	$4\text{-}IC_6H_4OCH_2Co^{III}$ (91)	72
		$C_6H_5OCH_2I$ (100)	17
		$C_6H_5OCH_2\text{-}ON{=}C(Me)\text{-}C(Me){=}NOH$ (106)	8
(33)	ICl	$4\text{-}IC_6H_4OCH_2Co^{III}$ (91)	57
		$C_6H_5OCH_2Cl$ (98) + $C_6H_5OCH_2I$ (100)	32
		$C_6H_5OCH_2\text{-}ON{=}C(Me)\text{-}C(Me){=}NOH$ (106)	10

....contd.

Table 2.4.A (contd.)

1	2	3	4
(34)	Cl_2	$4\text{-}ClC_6H_4NHCH_2Co^{III}$ (92)	56
		$C_6H_5NHCH_2Cl$ (101)	40
(34)	Br_2	$4\text{-}BrC_6H_4NHCH_2Co^{III}$ (93)	81
		$C_6H_5NHCH_2Br$ (102)	16
(34)	Br_2 (2)*	$4\text{-}BrC_6H_4NHCH_2Br$ (110)	80
		$C_6H_5NHCH_2Br$ (102)	16
(34)	I_2	$4\text{-}IC_6H_4NHCH_2Co^{III}$ (94)	85
		$C_6H_5NHCH_2I$ (103)	5
		$C_6H_5NHCH_2\text{-}ON{=}C(Me)\text{-}C(Me){=}NOH$ (107)	10
(34)	ICl	$4\text{-}IC_6H_4NHCH_2Co^{III}$ (94)	80
		$C_6H_5NHCH_2Cl$ (101) + $C_6H_5NHCH_2I$ (103)	5
		$C_6H_5NHCH_2\text{-}ON{=}C(Me)\text{-}C(Me){=}NOH$ (107)	10

*left for longer time (12-15 hrs.); $Co^{III} = Co^{III}(dmgH)_2Py$

Table 2.4.B: Spectral and Analytical Characteristics of X-  -Y-CH_2-$Co^{III}(dmgH)_2Py$ (86-94)

Compound No.	Y	X	^{1}H NMR Chemical Shift (δ): ($CDCl_3$)(ppm)						Analysis: Found (Calcd.), %				UV-vis: λ_{max} (nm) (CH_3OH)
			dmgH	Aromatic	$-CH_2$	Pyridine β	Pyridine γ	Pyridine α	C	H	N	X	
1	2	3	4	5	6	7	8	9	10	11	12	13	14
(86)	S	Cl	2.05	6.91-7.26	2.40	7.60	8.30	8.56	45.7 (45.5)	4.7 (4.8)	13.6 (13.3)	6.4 (6.7)	430, 381, 286, 232
(87)	S	Br	1.94	7.02-7.40	2.37	7.66	8.25	8.52	41.3 (41.1)	4.45 (4.3)	12.4 (12.2)	14.2 (14.0)	432, 283, 286, 232
(88)	S	I	1.98	6.82-7.32	2.22	7.56	8.26	8.50	39.2 (39.0)	4.12 (4.0)	8.4 (8.7)	19.4 (20.1)	231, 284, 280, 233
(89)	O	Cl	1.94	6.68-7.34	4.46	7.50	7.85	8.28	47.4 (47.1)	4.8 (4.9)	13.4 (13.7)	6.7 (7.0)	420, 320 250, 230
(90)	O	Br	1.90	6.76-7.38	4.30	7.64	8.14	8.36	43.6 (43.3)	4.2 (4.3)	12.3 (12.6)	14.1 (14.4)	430, 322 242, 230
(91)	O	I	1.84	6.80-7.32	4.20	7.70	7.85	8.41	40.4 (40.1)	4.0 (4.2)	11.3 (11.7)	21.0 (20.7)	436, 328, 254, 231

...contd.

Table 2.4.B (contd.)

1	2	3	4	5	6	7	8	9	10	11	12	13	14
(92)	NH	Cl	1.96	6.69-7.40	4.66	7.40	7.62	8.16	47.1 (47.2)	5.3 (5.1)	16.3 (16.5)	14.2 (14.3)	457, 318, 282, 242
(93)	NH	Br	1.91	6.52-7.31	4.46	7.54	7.52	8.20	43.2 (43.4)	4.8 (4.7)	15.7 (15.2)	14.4 (14.5)	459, 321, 288, 240
(94)	NH	I	1.90	6.51-7.30	4.30	7.20	7.64	8.10	40.4 (40.2)	4.1 (4.3)	14.1 (14.0)	22.1 (22.4)	457, 326, 276, 238

Table 2.4.C: Characteristics of the Organic Products (95-103) and (108-110) from Reaction of Halogens with $PhY-CH_2-Co^{III}(dmgH)_2Y$ (Y = S, O, NH) (32-34)

Compound[c] No.	B.P. (°C)	^1H NMR Chemical Shift (δ): ($CDCl_3$) (ppm)		UV: λ_{max} (nm) (CH_3OH)
		Aromatic	CH_2	
(95)	66 /0.2 mm	7.42(m)	4.91(s)	247
(96)	82 /0.2 mm	7.31(m)	4.82(s)	249, 239
(97)	b	7.26(m)	4.56(s)	251, 226
(98)	92 /20 mm	6.82-7.30(m)	5.82(s)	259
(99)	110 /20 mm	6.9-7.4(m)	5.92(s)	254
(100)	173 /14 mm	6.98-7.40(m)	6.01(s)	253
(101)	203 sub	6.68-7.30(m)	3.38(s)	240, 247
(102)	a	6.70-7.20(m)	3.46(s)	240, 249
(103)	a	6.76-7.30(m)	3.90(s)	240, 252
(108)	a	7.06-7.51(m)	4.76(s)	249, 238
(109)	a	7.06-7.54(m)	5.85(s)	254
(110)	a	6.86-7.26(m)	3.40(s)	241, 247

a) compounds unstable; b) low melting solid; c) all compounds give satisfactory halogen analyses.

Table 2.4.D: Characteristics of PhY-CH_2-ON=C(Me)-C(Me)=NOH (105-107)

Compound No.	Melting Point (^oC)	^1H NMR: (δ): ($CDCl_3$)(TMS)			UV: λ_{max} (nm)
		Aromatic	$-CH_2$	dmgH	(CH_3OH)
(105)	101	7.26, 7.40	5.54	2.24, 2.28	312
(106)	99	7.35	5.95	2.22, 2.30	222
(107)	74	7.30, 7.46	5.20	2.24, 2.27	228

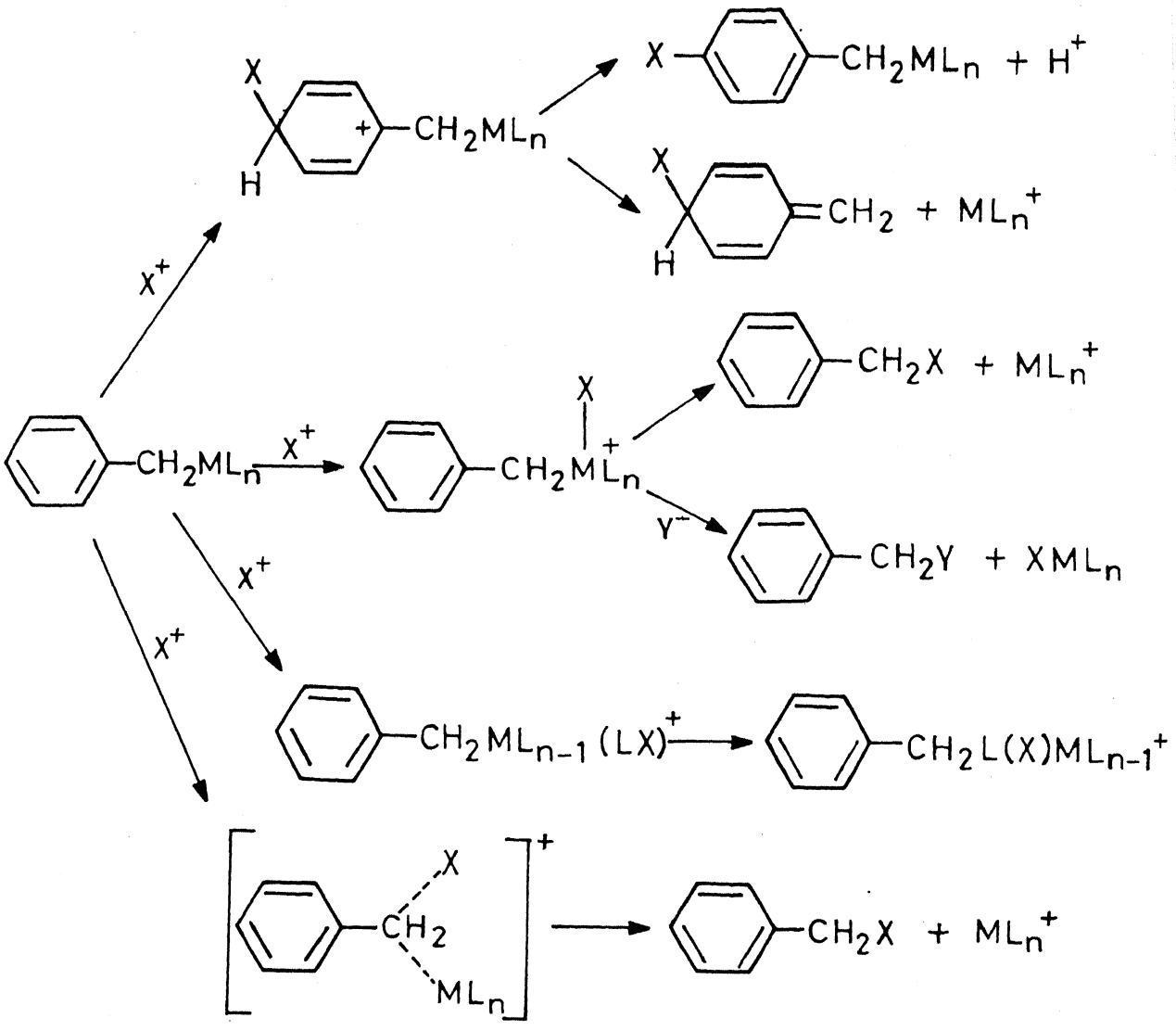
the presence of equimolar amount of anisole forms (90) and (99) and anisole is totally recovered back.

The ^{1}H NMR spectra and other characteristics of organometallic products, organic products, dimethylglyoxime mono ethers are given in Tables 2.4.B, 2.4.C and 2.4.D, respectively.

2.4 Discussion

In principle an electrophile may attack a benzyl metal complex ($PhCH_2ML_n$) at a variety of sites[152] (Scheme 2.5). Attack may take place at the benzene ring leading either to substitution[305] (Eq. 1) and/or to the metal carbon-bond cleavage[306] (Eq. 2), attack may take place at the metal[307] centre leading to a variety of products including those from a reductive elimination process (Eq. 3) and from nucleophilic displacement at the α-carbon (Eq. 4), attack may take place at ligand L leading to a variety of products including those from insertion process[308] (ligand migration) (Eq. 5), and attack may also take place directly at α-carbon[309] (on the carbon-metal bond orbital) (Eq. 6). Reactions of all six types are known an the path followed is clearly a function of the particular electrophile, its interaction with HOMO of the complex and the nature of the reaction medium. In all cases a certain degree of electron transfer occurs.[159,202,209,310,311]

Scheme 2.5



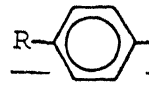
In general, chlorine is more reactive than bromine and iodine is relatively unreactive. Thus, whilst most aromatic compounds may be halogenated by molecular chlorine and bromine, there is no clear cut case of iodination by molecular iodine. Much of the information about the mechanism of these reactions has come from broad comparisons of reactivity and from product studies,[312]

despite the fact that the order of reaction with respect to halogen is frequently greater than one, particularly in the case of reaction of bromine in acetic acid. Only at low bromine concentrations in acetic acid, are these substitutions first order in the halogen. Therefore, all the reactions described in the present work are carried out by the very slow addition of the dilute bromine/chlorine solutions to the benzylcobaloxime solution in order to keep the halogen concentration as low as possible. Under such conditions, reactions of higher order in halogen should be negligible and the comparison between substitution and carbon-cobalt bond cleavage should be more meaningful. However, if the reactions are carried out with higher concentration of halogen than are used here, other products may well be obtained.

Johnson et al. found that the bromination of benzyl cobaloxime (17) by molecular bromine formed $\geqslant$90% benzyl bromide while chlorination gave 62% benzyl chloride and 38% of benzyl ether of dimethylglyoxime[299] (71). Similar monoethers of dimethylgloxime have been shown to form as a side product in the reaction of organocobaloximes with various electrophilic oxidizing agents.[153] However, no explanation was offered then. In subsequent studies, the formation of this byproduct was suggested to arise as a result of an oxidative dealkylation mechanism consisting of a nucleophilic displacement of cobalt from the organocobalt(IV) species formed *in situ*.[313] This

suggestion was later supported by Halpern et al.[138] who also confirmed the existence of organocobalt(IV) species which is quite stable at -70°C and undergoes nucleophilic substitution by a variety of nucleophiles. The stability of organocobalt(IV) has recently been reviewed by Volpin et al.[145]

Recently, Tauzer et al. have preferred the electrophilic mechanism in the halogenation study of benzyl cobaloxime with ICl and ICl_2.[275] They have made further generalizations that other benzyl cobaloxime derivatives will also react via a similar mechanism although they studied only benzyl cobaloxime. Since halogenations are among those reactions whose rates are most susceptible to the nature and number of substituents in the benzene ring,[314] it is anticipated that ring substitution may take place if the metal containing groups are supplemented by the electron donating groups.[299] Furthermore, in view of the following chemical oxidation potential data on various substituted benzyl cobaloximes which vary significantly with the nature of theaxial organic ligand (Table 2.5, p.135) it is expected that a systematic study on the substituted benzyl cobaloximes might help in differentiating between the many proposed mechanisms in literature. In this process, the effect of substitution into the benzene ring on the Co-C bond cleavage process is also taken into account.

2.4.1: System I-  $-CH_2-Co^{III}(dmgH)_2Py$ (R = Me, $CHMe_2$, CMe_3, Br, Cl, CN, CHO, COOH, NO_2)

We find that the substitution of the inductively electron releasing groups like methyl, isopropyl and t-butyl into the para-position of benzene ring (18, 19 and 20, respectively) do not enhance the reactivity of benzene ring as compared to the faster Co-C bond cleavage and corresponding benzyl halides (40-45) are the exclusive organic products formed in their reaction with Br_2 and Cl_2*. Besides, no trace of dimethylglyoxime ether product is detected in any case.

However, in the reaction of halogens with 4-bromo (21), 4-chloro (22), 4-cyano (23), 4-formyl (24), 4-carboxyl (25) and 4-nitro (26) benzyl cobaloximes, both benzyl halides (46-57) and benzyl ether of dimethyl glyoxime (72-77) are formed in varying proportions. The formation of the ether products points to the existence of organocobalt(IV) species in such reactions since it has been observed earlier that such a cobalt(IV) species predominantly decomposes to such products especially in the absence of a nucleophile. A free radical mechanism has been proposed for such dmg-ether formation.[315]

The observations

i) that the extent of the formation of ethers (71-77) is greater in chlorination than in bromination,

*It is to be noted that some dissociation of pyridine from cobalt is known to occur in acetic acid and the effects described are in part due to $-CH_2Co^{III}(dmgH)_2$.solvent. However, such a change is unlikely to have a major effect on the character of the substituent.

ii) the formation of mixed halides when

(a) chlorination is carried out in the presence of bromide ions, (b) bromination in the presence of chloride ions, all poin to the oxidative dealkylation mechanism in such reaction. The results can be further explained as follows:

Since chlorine is a better oxidising agent than bromine, it will oxidise the complex fairly rapidly and completely, may be much before nucleophilic displacement and ether formation takes place, whereas bromine may not oxidise the complex quite as completely. Since chloride ion is a much weaker nucleophile than bromide ion, any competition between nucleophilic displacement (a second order process) and ether formation (probably a first order process) will favour the ether formation in the case of weaker chloride ion. The higher reactivity of chlorine as compared to bromine is as expected and is justified keeping in view the similarities of the reduction potential of $[4\text{-}RC_6H_4\text{-}CH_2Co^{IV}(dmgH)_2Py]^+$ /$4\text{-}RC_6H_4CH_2Co^{III}(dmgH)_2Py$ (ranges between 0.77 and 1.06 V) and that of Br_2/Br^- (E = 0.82 V). It is quite likely that some $4\text{-}RC_6H_4CH_2Co^{III}(dmgH)_2Py$ and Br_2 may be formed through the oxidation of Br^- by $[4\text{-}RC_6H_4CH_2Co^{IV}(dmgH)_2Py]^+$. However, the corresponding Cl_2/Cl^- potential is quite high (E = 1.1 V), so as to preclude oxidation of Cl^- to Cl_2 under the reaction conditions. It seems from $E_{1/2}$ values of these organocobaloximes that the tendency of oxidation to organo-

cobalt(IV) species increase with the donor strength of the substituent in the benzene ring. The exclusive formation of benzyl halides alone in (18-20) may look surprising. However, it is not really surprising if one considers the life time of the transient $4\text{-}RC_6H_4CH_2Co(IV)$ species in solution and its rate of reaction with the nucleophilies. A qualitative information on this point is available from Halpern's work and is outlined in Table 2.5. It is clear from the rate data that the transient $4\text{-}MeC_6H_4CH_2Co(IV)$ undergoes nucleophilic substitution much faster (atleast by 12 times) as compared to $C_6H_5CH_2Co(IV)$, hence the substitution product must be the major product or the only product in the former. Similarly, $4\text{-}NO_2C_6H_4CH_2Co(IV)$ which reacts much slower with the nucleophiles will tend more to decompose to the ether product and hence the latter will form in much higher proportions. Therefore, the formation (20%) of ether product (77) even with bromine is not really surprising in this case. Keeping the above explanation in mind, the formation of benzyl halides (38-57) and dimethylglyoxime ether (71-77) in varying proportions is easily explained.

The formation of mixed halides when chlorinations are carried out in the presence of bromide ion and the formation of the higher proportions of 4-nitrobenzyl bromide and the lower proportions of dmgH-ether when the same is done in the presence of large excess of bromide ion can be explained as follows: Chlorine being a better oxidant, apart from oxidising the cobal-

Table 2.5: Thermodynamic and Kinetic Parameter for the Oxidation of $[4\text{-}RC_6H_4CH_2Co^{III}(dmgH)_2.H_2O]$*

R	$E_{1/2}$ [V]‡ vs SCE[a]	k_7 [L $mol^{-1}sec^{-1}$][b]	K_7[c]	k_8 (sec^{-1})	Life time $1/k_8$ (sec)[d]
H (17)	0.859	5.0×10^4	2.8×10^{-1}	8.3	0.12
CH_3 (18)	0.849	1.4×10^5	3.9×10^{-1}	10^2	0.01
Cl (22)	0.876	1.0×10^4	1.7×10^{-2}	1.7	0.58
CN (23)	0.800	-	-	-	-
CHO (24)	0.870	-	-	-	-
NO_2 (26)	0.907	1.0×10^2	3.2×10^{-3}	1.7×10^2	58.8

* All values except for (23 and 24) are taken from ref. 316.

‡ With axial ligand, pyridine, values are little lower.

a) Relative to saturated calomel electrode, measurement at 25°C is aqueous 1.0 M $NaClO_4$ adjusted to pH 2.0 with $HClO_4$.

b) Chemical oxidation by $[IrCl_6]^{2-}$ according to the following Equations:

$$[4\text{-}RC_6H_4CH_2Co^{III}] + [IrCl_6]^{2-} \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} [4\text{-}RC_6H_4CH_2Co^{IV}]^+ + [IrCl_6]^{3-} \quad .. (7$$

$$[4\text{-}RC_6H_4CH_2Co^{IV}]^+ + H_2O \xrightarrow{k_8} [Co^{II}] + ROH + H^+ \quad .. (8$$

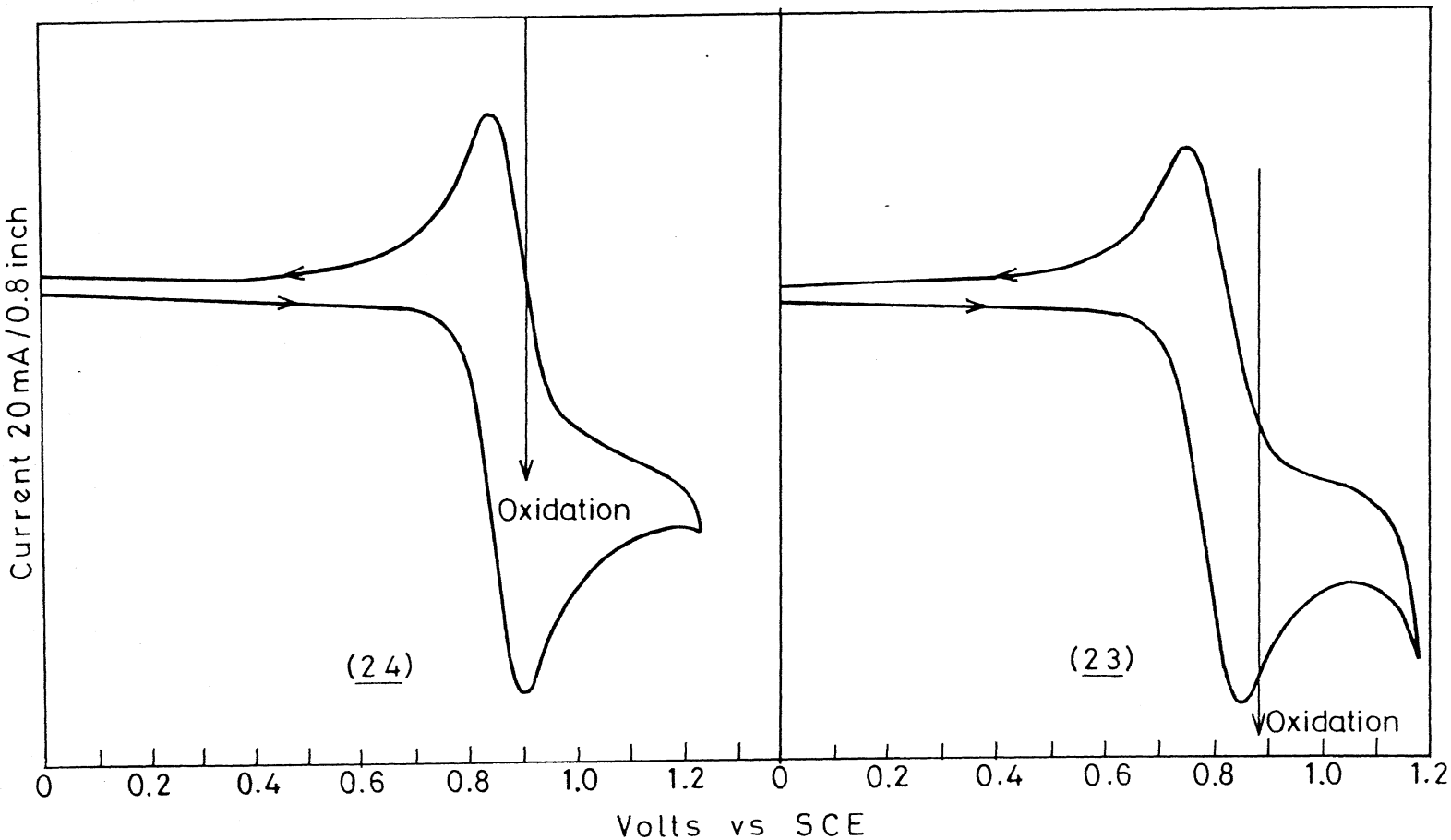
$$[4\text{-}RC_6H_4CH_2Co^{III}] + [IrCl_6]^{2-} + H_2O \longrightarrow [Co^{II}] + ROH + [IrCl_6]^{3-} +$$

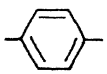
$$\frac{-d[4\text{-}RC_6H_4CH_2Co^{III}]}{dt} = \frac{k_7k_8\,[4\text{-}RC_6H_4CH_2Co^{III}][IrCl_6]^{2-}}{k_{-7}\,[IrCl_6]^{3-} + k_8}$$

c) $K_7 = k_7/k_{-7}$

d) Life time = $1/k_8$ of RCo^{IV}

Co = $Co(dmgH)_2.H_2O$



CYCLIC VOLTAMMOGRAM OF R-  -CH_2-Co^{III} $(dmgH)_2$ Py, R = CHO (24), R = CN (23), SCAN RATE 50 mV S^{-1}

oxime, it will react with bromide ion to give Cl^- and BrCl. In the presence of more bromide ion, it will form Cl^- and Br_2. This is, therefore, merely changing the halogen progressively making it Cl_2, BrCl and Br_2, thus, a weaker oxidising agent. In the process, the amount of halide ion is increased, hence, the decrease in ether formation. The complete scheme can be written as follows:

$$ArCH_2Co^{III}(dmgH)_2Py + X_2 \longrightarrow ArCH_2Co^{IV}(dmgH)_2Py^+ + X_2^{\cdot-} \quad .. (9)$$

$$X_2^{\cdot-} \longrightarrow X^- + \dot{X} \quad .. (10)$$

$$ArCH_2Co^{III}(dmgH)_2Py + \dot{X} \longrightarrow ArCH_2Co^{IV}(dmgH)_2Py^+ + X^- \quad .. (11)$$

$$ArCH_2Co^{III}(dmgH)_2Py + \dot{X} \longrightarrow ArCH_2X + Co^{II}(dmgH)_2Py \quad .. (12)$$

$$ArCH_2Co^{IV}(dmgH)_2Py^+ + X^- \longrightarrow ArCH_2X + Co^{II}(dmgH)_2Py \quad .. (13)$$

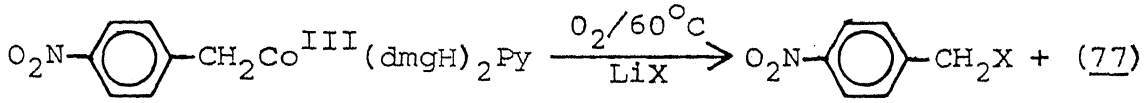
$$Co^{II}(dmgH)_2Py + X_2 \longrightarrow XCo^{III}(dmgH)_2Py + X^- \quad .. (14)$$

$$\dot{X} + Co^{II}(dmgH)_2Py \longrightarrow XCo^{III}(dmgH)_2Py \quad .. (15)$$

$RCo^{III}(dmgH)_2Py$ is oxidised to $RCo^{IV}(dmgH)_2Py^+$ and the other product in this oxidation process is $X_2^{\cdot-}$ (Eq. 9) which breaks into X^- and $\dot{X}$ (Eq. 10). The fate of X^- (Eq. 13) has been discussed above, however, $\dot{X}$ can do several things including oxidising more RCo^{III} to RCo^{IV} (Eq. 11) or may act as a displacing radical (Eq. 12). Equation (14) will occur only if $Co^{II}(dmgH)_2Py$ is formed in the presence of excess X_2. At this stage we are

not sure as to what really happens to the radicals but it is certain that the halogenation of cobaloximes seems to proceed with a complicated reaction mechanism.

The following result provides unambiguous support for the oxidative dealkylation mechanism since 4-nitrobenzyl halide can come about only by a nucleophilic attack on the oxidised organocobalt(IV) species formed *in situ*.



(X = Cl or Br) (X = Br, 56; X = Cl, 57)

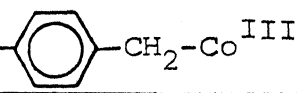
Interestingly, this reaction forms one of the first examples in cobaloxime chemistry where the organocobaloxime is oxidised rather than oxygenated by molecular oxygen.*

It appears that our results point to the oxidative dealkylation mechanism and donot conform with the generalisations made by Tauzher et al.[275] These results further indicate that even a small difference in the oxidation potential realised on varying the substituent in the benzene ring is sufficient enough to cause a general variation in the product formation. It is, however, very difficult to know at this stage that out of the

---

*It is also observed that in the absence of LiX, $4\text{-}NO_2C_6H_4CH_2\text{-}Co^{III}(dmgH)_2Py$ at $60^\circ/O_2$ does not undergo any oxygen insertion into Co-C bond.

total benzyl halide formed in each reaction, how much is the real contribution from the oxidative dealkylation mechanism, as it is likely that a direct electrophilic mechanism is also occurring at the same time. Besides, the Co-C bond in organocobaloximes is very susceptible to homolytic cleavage, the formation of benzyl halide by such a process to whatever extent may also contribute to the overall yield, although, all precautions have been taken to avoid such a process.

2.4.2: System II-  ($R = NHCOCH_3$, NMe_2, OCH_3)

In the above discussion, one specific point has not been taken into account, i.e., in the process of activating or deactivating the benzene ring in the organocobaloxime (17-26), it is quite likely that the competitive Co-C bond cleavage may also get affected by such substituents. It is suggested in the literature that the effect of any substituent in the para-position of benzene ring is transmitted to cobalt through methylene group but such an effect is not transmitted effectively through σ bond.[222,299] It is, therefore, anticipated that irrespective of the substituent in the para-position (inductive groups only) a similar reactivity of Co-C bond cleavage should be observed. This is clearly reflected in our results where the Co-C bond reactivity is similar for all compounds (17-26) (reaction time is identical for all cases). Therefore, results

of (17-26) are justified.

Interestingly, the substitution by conjugatively electron releasing group like -OMe, $-NHCOCH_3$ and $-NMe_2$ in the para-position of benzene ring should increase the electron density at the Co-C bond by an effective π contribution. The study of such systems, therefore, should shed more light on the Co-C cleavage mechanism.

Three mechanisms (Fig. 4) have been proposed in the literature for the attack of electrophile at a saturated carbon centre i.e., at the carbon-cobalt bonding orbital leading to the cleavage of Co-C bond.[317]

One must consider the following two factors:

(1) Activation of the aromatic ring by these substituents, and

(2) The increase in the π-electron density at the Co-C bond.

The second factor is important since the effect of substituent in the benzene ring is very effectively transmitted to the Co-C bond by conjugation. This increases the π-electron density at carbon bound to cobalt and hence should lead to a faster attack of electrophile on carbon especially if pathway 'C' is predominantly operating. However, if it is pathway 'A' which is occurring via σ skeleton, the increase in π-electron density should not make any difference to Co-C cleavage process. One

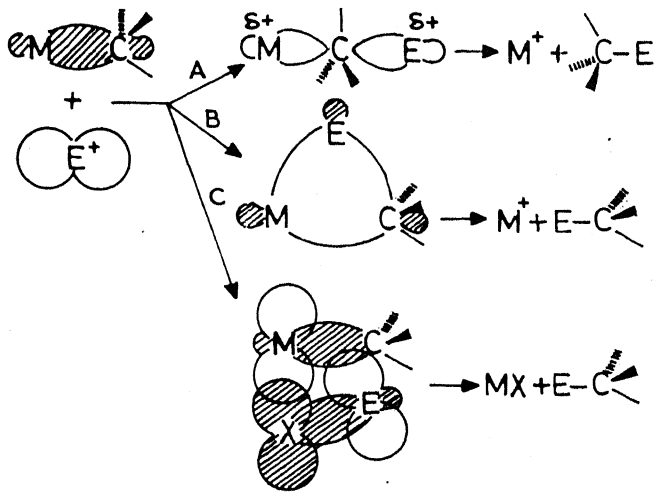


FIG. 4

Reproduced from ref. 317.

must also consider Pratt's view that any increase in the electron density at the α carbon affects the Co-C bond strength by coulombic repulsions.[35]

Furthermore, it must be remembered that the Co-C bond cleavage is directly competing with the ring substitution having enhanced electron density in the benzene ring by both $-CH_2Co^{III}(dmgH)_2Py$ and R group (R = OMe, $NHCOCH_3$, NMe_2). Moreover, it is generally found that the influence of conjugatively electron releasing groups on the ring substitution is markedly greater than their influence on the side chain reactions as shown by the much greater values of the Brown $\sigma+$ constants and the Hammetts σ constants for such substituents and by the generally larger values of ρ for such substitution reactions.[317] It will therefore be interesting and useful to study the halogenation in cobal-

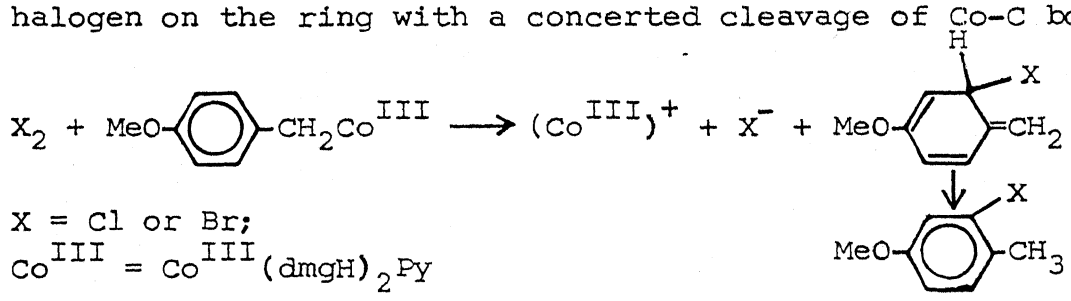
oximes of the type $4\text{-}RC_6H_4CH_2Co^{III}(dmgH)_2Py$ (R = $NHCOCH_3$, NMe_2, OMe;(27), (28), (29), respectively).

In the reaction of (27) and (28) with halogens (Br_2 and Cl_2) both organic (58-62) and organometallic products (80-83) are formed in varying proportions indicating a competition between the ring halogenation and Co-C cleavage (Scheme 2.3, p. 109). The organic product, 4-N,N-dimethylbenzyl chloride (from 28 with Cl_2) is highly unstable and is, therefore, isolated and characterised by its reactions with thiophenol/Et_3N. Owing to the very compact nature of the aromatic proton resonances in organometallic products (80-83), the position of halogen is very difficult to assign accurately. Moreover, the organic product obtained after the bromination of the organometallic product (83) under photolytic conditions also does not help in the assignment of the position of bromine in the ring. Only one halogen is found to enter into the aromatic ring and all attempts to put the second halogen into the organometallic products (80-83) fail and result in the cleavage of Co-C bond. This is not surprising since the halogen deactivates the ring towards further ring halogenation and hence the cleavage of Co-C bond results. A careful monitoring of the reaction of (27) with Br_2 at regular intervals of 10 minutes indicates that both organic and organometallic products are formed simultaneously.

This is to be noted again that the relative ease of Co-C bond cleavage in (27) and (28)[reaction time $\simeq$ 0.5 hr compared

to the reaction time 3 hrs in (17-26)] substantiates further the relative importance of pathway 'C'. The near absence of dimethylglyoxime ether product is noteworthy. In view of this, a direct electrophilic mechanism seems to be the most favourable process.*

In contrast, the halogenation of 4-methoxybenzyl cobaloxime (29) forms exclusively the ring halogenated toluene (63 & 64), a product observed for the first time in such studies.‡ The exclusive formation of this isomer alone and the complete absence of other isomer where halogen is ortho to methoxy group points to the more activating effect of $-CH_2Co^{III}(dmgH)_2Py$ group than methoxy. The products (63) and (64) may probably arise by the attack of halogen on the ring with a concerted cleavage of Co-C bond.



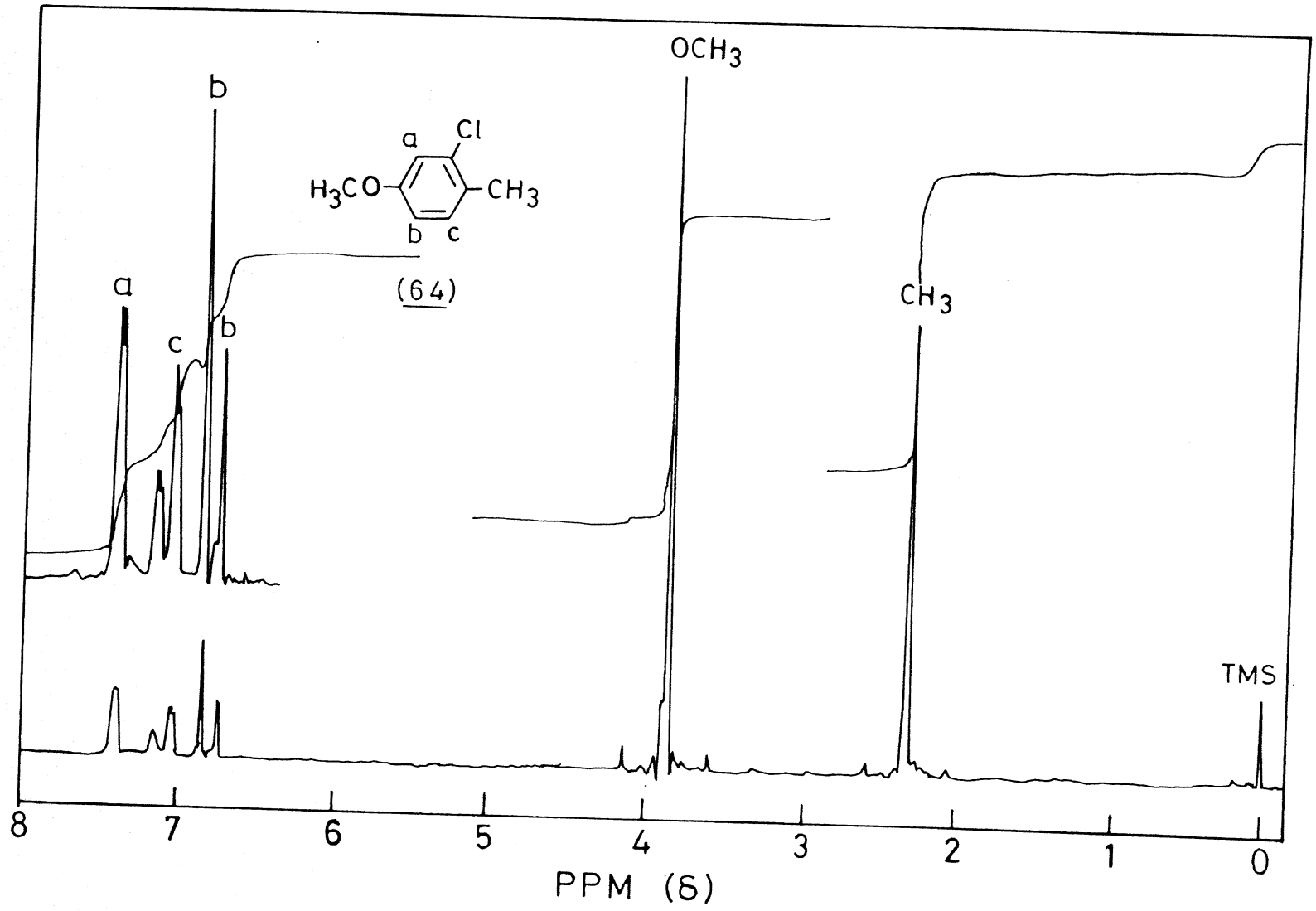
X = Cl or Br;
$Co^{III} = Co^{III}(dmgH)_2Py$

---

*Though <5% dmgH ether formation is detected which may point to the little contribution of oxidative dealkylation process.

‡(a) It is to be noted that (29) forms 4-methoxybenzyl iodide with I_2 at 40°C in dark. This arises partly from the inert character of I_2 towards electrophilic substitution of aromatic ring and the high electron affinity of iodine.[209]

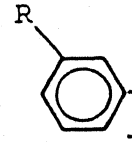
(b) The synthesis of (63) and (64) in quantitative yield by this procedure may become valuable since other methods of preparation are lengthy and low yielding (e.g., M.S. Carpenter and W.H. Easter, J. Org. Chem., 20 (1955) 401.)



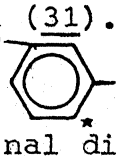
^1H NMR SPECTRUM (80 MHz) OF (64)

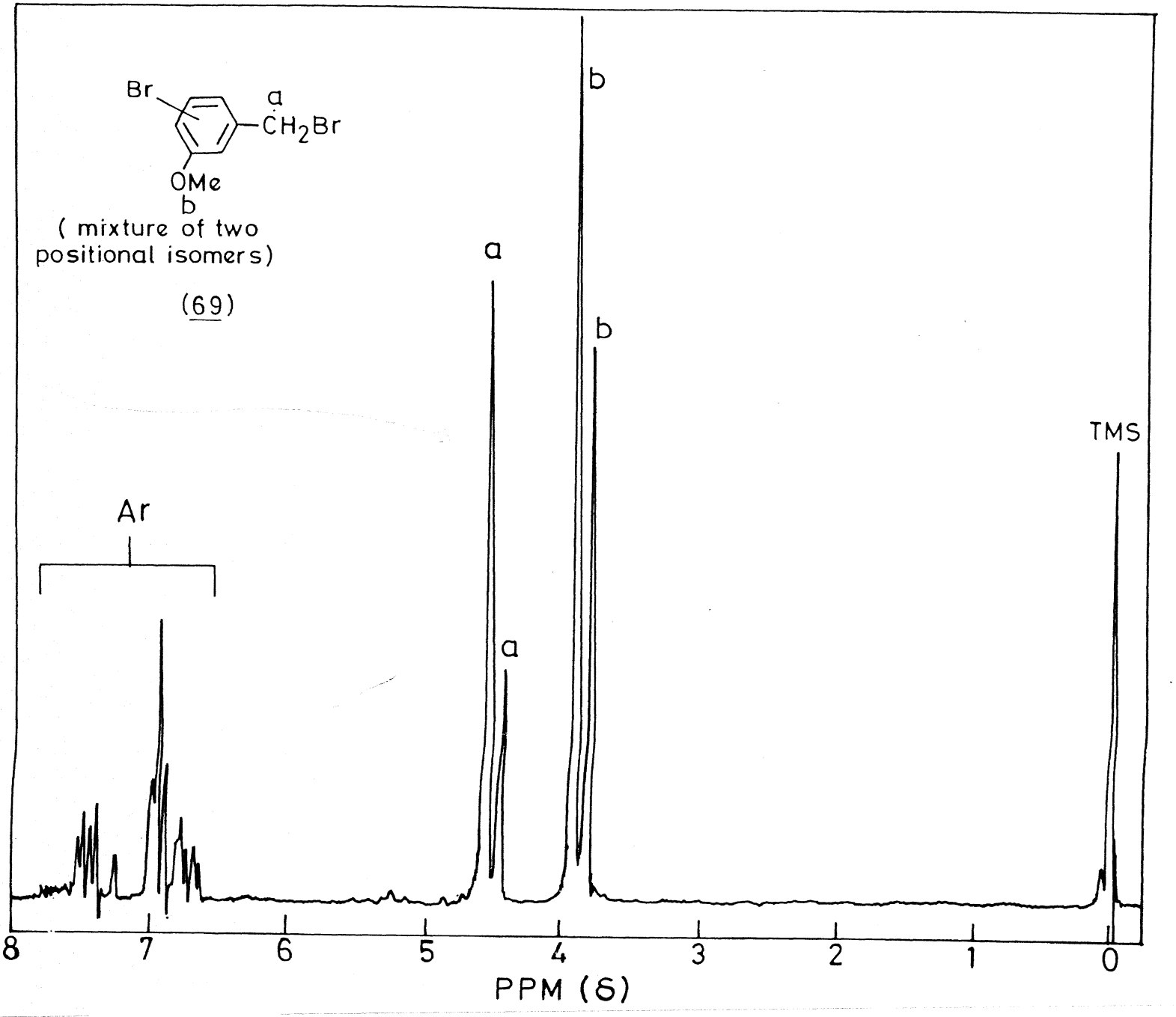
The possibility that bromination occurs without cleavage and then the HBr present may cleave the Co-benzyl bond, is ruled out since the reaction of (29) with pure HBr in chloroform under identical reaction conditions is very slow and does not form any 4-methoxytoluene, though the Co-C bond cleavage takes place on prolonged standing (4 days). Furthermore, the same product (63) is formed even when the reaction of (29) is carried out with Br_2 in the presence of K_2CO_3. A similar observation is made in the reaction of (27) and (28) where the HBr produced in the reaction does not effect the Co-C bond cleavage within the reaction time.

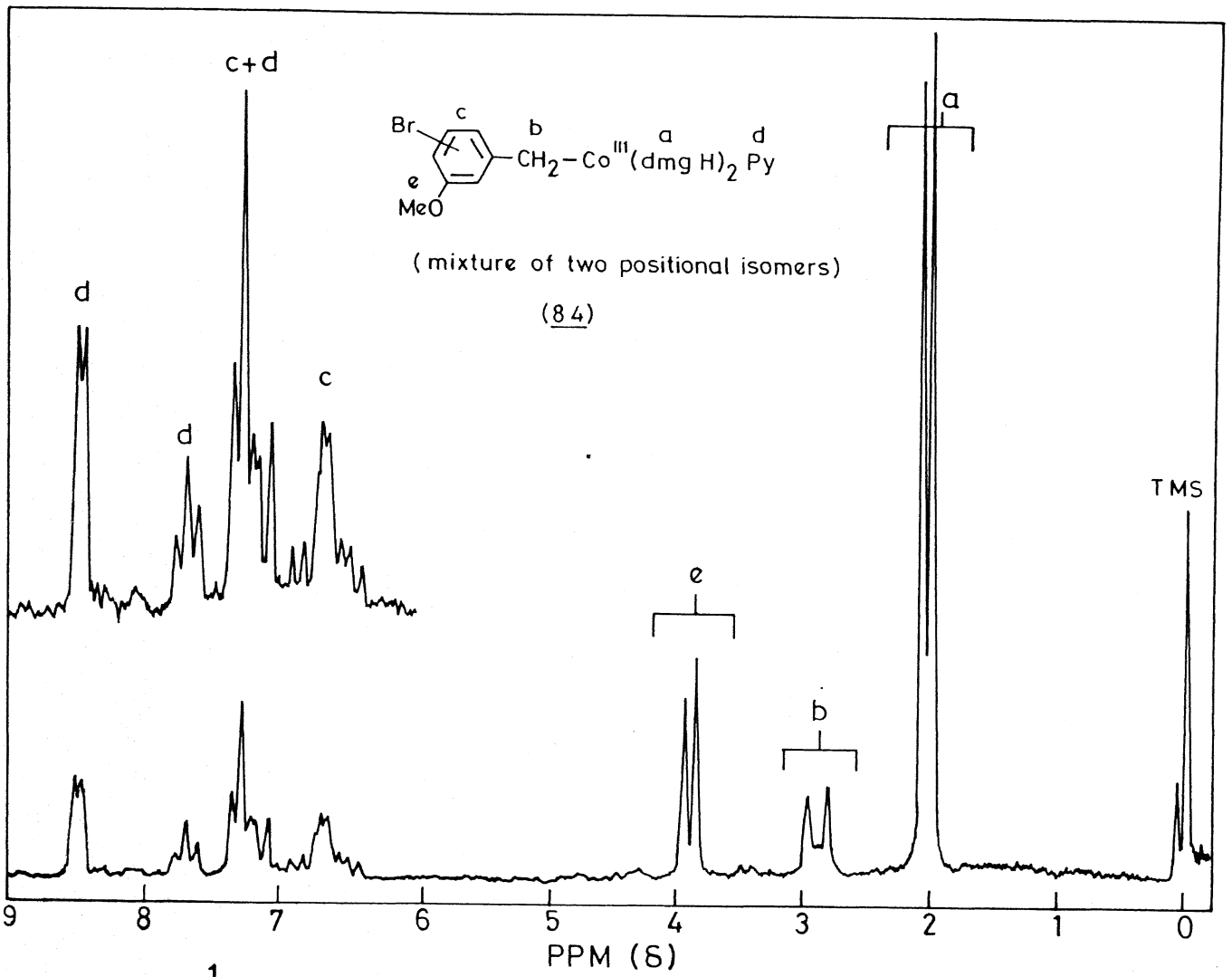
It is clear from the above discussion that conjugatively electron donating groups like $-NMe_2$, $-NHCOCH_3$, -OMe, are contributing to a large degree towards the ring halogenation. However, the effect of such a group when present at para-position is also transmitted to the metallomethyl group through extended conjugation and hence favours the competitive Co-C bond cleavage also.

2.4.3: System III-  $-CH_2Co^{III}(dmgH)_2Py$ (R = Me, OMe)

It is expected that the substitution of such a group at meta-position will completely inhibit such extended conjugation and should not favour the Co-C bond cleavage. However, the corresponding ring substitution should be more facile. The results indicate that the meta-substitution seems to be more effective in causing the ring substitution, for example, in the

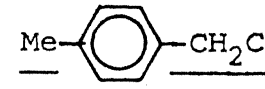
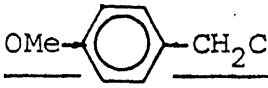
bromination of 3-methylbenzyl cobaloxime (30), both 3-methylbenzyl bromide (65) and 6-bromo-3-methylbenzyl bromide (66) are formed in equal proportion. The product distribution indicates that 50% reaction involves an initial attack of Br_2 on the ring followed by Co-C cleavage and 50 % reaction involves direct Co-C cleavage prior ring substitution. 3-Methylbenzyl bromide is inert to bromination under reaction conditions. 3-Methoxybenzylcobaloxime (31) on the other hand, forms ring substituted organic product (69, 70) and organometallic products (84, 85). Each of these products is a mixture of two positional isomers as indicated by ^1H NMR and all efforts to separate them by chromatography have failed. Hence, no clear cut comment on the comparison of the substituent effect can be made. A careful monitoring of the reaction [31 with Br_2] after every five minutes shows that both organic and organometallic products are formed simultaneously. A complete absence of 3-methoxybenzyl bromide points that no direct Co-C cleavage of the parent cobaloxime (31) takes place (such a product if at all forms, is inert to further bromination). It is certain from the product distribution that the initial attack of halogen is in the ring followed by Co-C bond cleavage. The formation of two positional isomers is not really surprising if one takes into account the electron densities in the ring in (31). For example, both positions marked * in the structure  density. The marginal difference between these two positions depends upon the overall activating effect of $-CH_2Co(III)$ vs OMe.


Br
a
CH2Br
OMe
b
(mixture of two positional isomers)
(69)
a
b
b
a
TMS
Ar
8
7
6
5
4
3
2
1
0
PPM (δ)



^1H NMR SPECTRUM (90 MHz) OF (84)

In view of our observation in case of 4-methoxybenzyl cobaloxime where $-CH_2Co^{III}(dmgH)_2Py$ is found to be more activating than OMe, we think that the isomer formed in higher proportion (65%) should favour the halogen ortho to $-CH_2Co^{III}(dmgH)_2Py$ group. Furthermore, since the reaction is almost instantaneous and probably approaches the encounter rate, the ratio of the organic and organometallic product depends upon the concentration and the mode of addition of halogen. The complete absence of the corresponding dimethylglyoxime ether product is once again noteworthy.

2.4.4: System IV-  and 

Interestingly, the protonation of dimethylglyoximato ligands in organocobaloximes has a marked influence on the reactivity at the Co-C bond and hence changes the course of reaction with halogens. For example, bromination of 4-methylbenzyl cobaloxime (18) forms exclusively 4-methylbenzyl bromide whereas the same reaction in the presence of 20% H_2SO_4, when monoprotonated species is the reactive species,‡ forms substantial amount ($\geqslant$90%) of 4-methylbenzyl ether of dimethylglyoxime. Only very little amount ($\leqslant$ 10%) of 4-methylbenzylbromide is formed. Ether is formed by the predominance of the

‡It is known that diprotonation takes place only at a much higher acidity.[317]

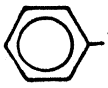
following reaction:

$$4\text{-}MeC_6H_4CH_2Co(dmgH)(dmgH_2)aq.^{+} + H^{+} \longrightarrow$$

$$4\text{-}MeC_6H_4CH_2ON{=}CMe\text{-}CMe{=}NOH + Co^{II} + dmgH_2$$

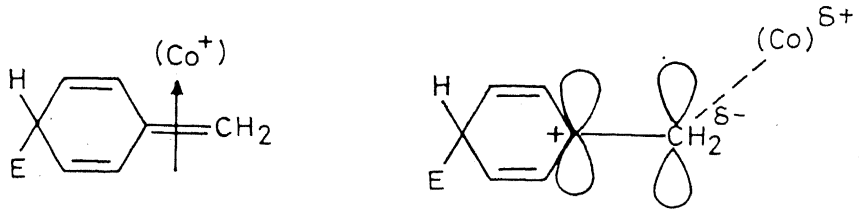
The ratio of the two products (ether:bromide, 70:30) changes in favour of bromide when the same reaction is done with the isolated monoprotonated complex, $4\text{-}MeC_6H_4CH_2Co(dmgH)(dmgH)_2aq.^{+}$ (no aq. H_2SO_4 is present in reaction). It indicates that the cleavage of Co-C bond by bromine is equally an important reaction in this case.

Similarly, BF_2 bridging of the equatorial ligands has a remarkable effect on the Co-C bond cleavage. The formation of $4\text{-}OMeC_6H_4CH_2Br$ and complete absence of the ring substituted toluene is noteworthy, indicating that Co-C bond cleavage is very facile in this case.

2.4.5: System V-  $YCH_2Co^{III}(dmgH)_2Py$ (Y = S, O, NH)

From the above studies, a general understanding about the effect of organic substituent towards the ring halogenation versus Co-C bond cleavage has been established. The strong electron donating character of the organometallic group $-CH_2-Co^{III}(dmgH)_2Py$ has also been confirmed and is attributed to a conjugative interaction. However, no attempt has been made so far to illustrate the exact mechanism of such electron donation. Two possibilities of conjugative interaction can be

visualized as shown below:



A B

In A, the formation of a π-complex takes place, where the metal occupies a different position relative to the benzene nucleus in the initial and transition states. Formation of such a complex is less likely with cobalt in +3 oxidation state. In B, a vertical stabilization is achieved following a σ-π overlap, the cobalt atom with its appendent ligands remains essentially in the same position relative to the benzyl group both in the initial and the transition state. For reactions which approach the encounter rate, the activation energy must be very low and hence the transition state must closely resemble the initial state. Under such conditions the conjugative electron donating effect of the $-CH_2-Co^{III}(dmgH)_2Py$ group is expected to operate via transition state B rather than A.

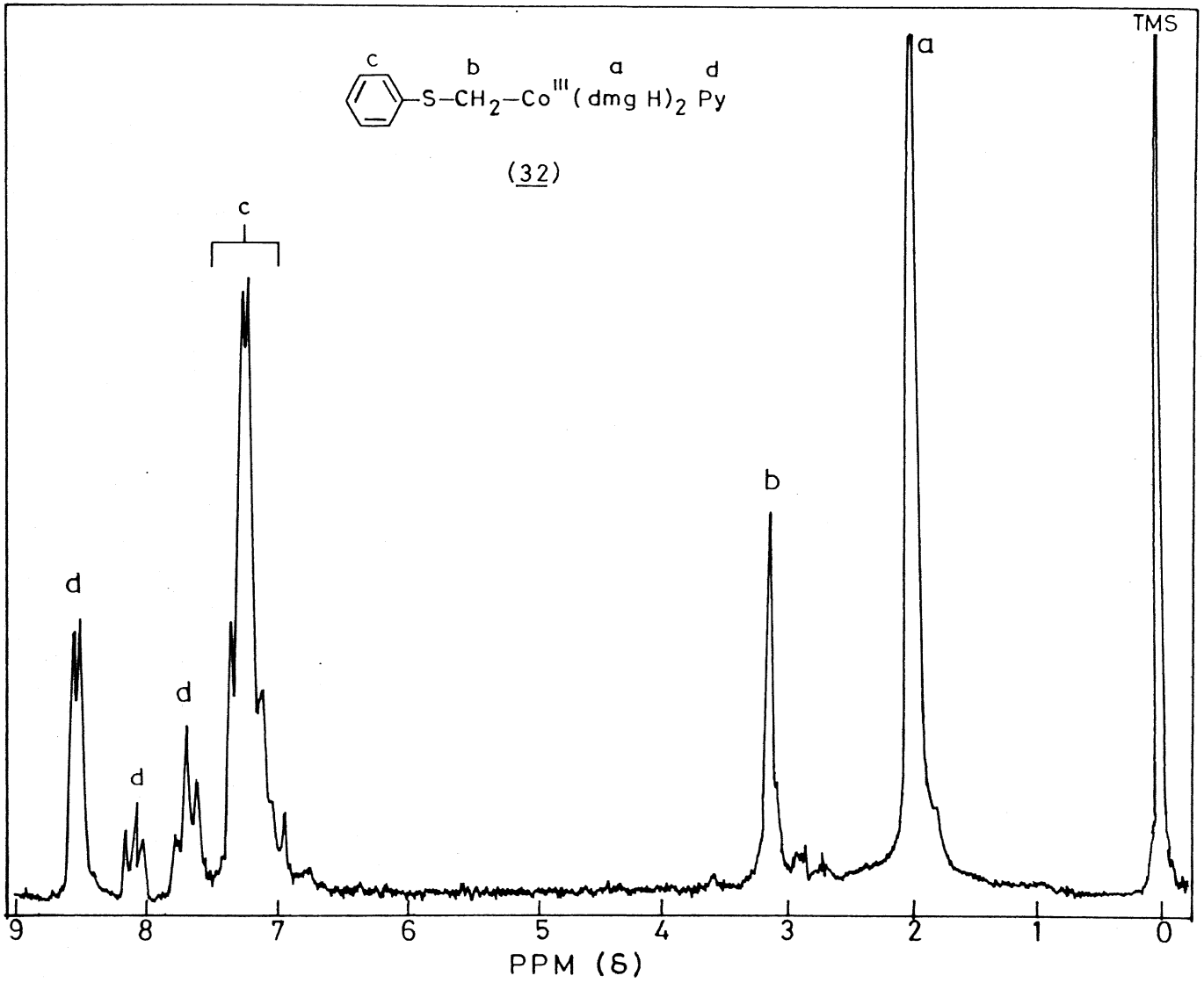
In order to focus on the exact mechanism of electron donation by the $-CH_2Co^{III}$ group and to provide further support for its conjugative nature, halogenation studies are done on the cobaloximes of the type $C_6H_5-Y-CH_2Co^{III}$ (Y = S, O, NH; 32-34). In these cobaloximes a facile transmission of the conjugative influence of the metallomethyl group to the aromatic ring via the lone pair on Y is expected, provided the σ-π mechanism is

operating. As a result of such extensive conjugation the π-electron density into the benzene ring should increase many fold as compared to simple benzyl cobaloximes. However, the electron density at C-Co bond is also expected to increase due to the electron donation by $-YC_6H_5$ group. One should, therefore, anticipate a remarkable competition between the ring halogenation vs Co-C cleavage which will effect the nature and yield of products from halogenation in these systems.

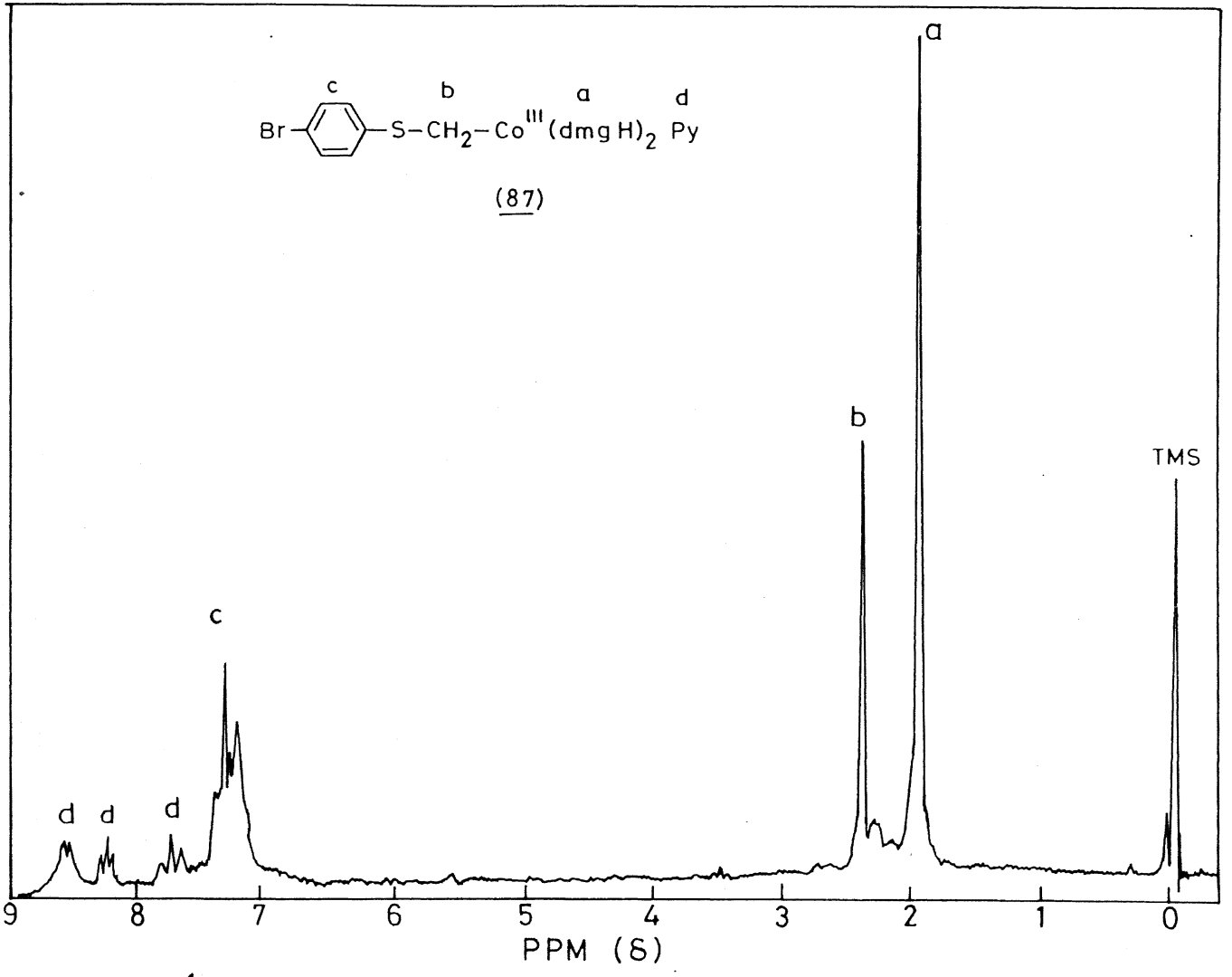
The reactions of (32-34) with Cl_2, Br_2 and I_2 result in the formation of ring halogenated cobaloximes (86-94) as the major products in all the cases indicating an enhanced π-electron density in the aromatic ring. However, one must further rationalise the results in light of the following:

i) Is hetero atom alone responsible for ring activation?
ii) Is it due to an extended conjugation (transitn. st. B, p.151)
iii) Is an alternative mechanism responsible?

(i) From the literature one finds that anisole is 10^4 times more reactive than toluene towards ring halogenation, which is attributed to the -M effect of oxygen in anisole. To quantify further such an effect of the heteroatom, an analogy can be drawn comparing the charge densities at different centres in $PhCH_2Cl$ and $PhOCH_2Cl$[318,319] (Table 2.6).



^{1}H NMR SPECTRUM (90 MHz) OF (32)



^1H NMR SPECTRUM (90 MHz) OF (87)

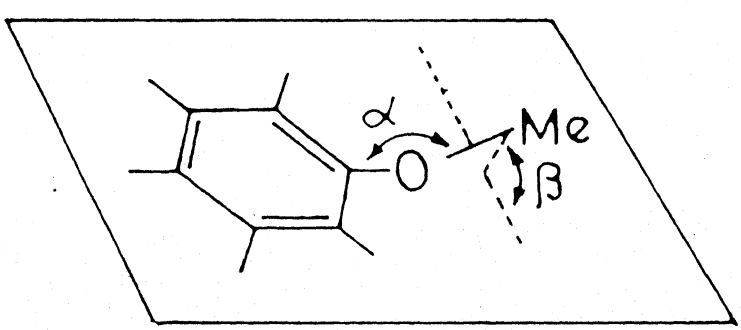
Table 2.6. Charge Density (in 10^{-4} electron) of Phenyl Carbons and Other Atoms in the Benzyl chloride and Benzyl ether along with Substituent Parameter σI & σR[318]

R	σ_I	σ_R	Excess pi-charge over 6 carbon atoms	Excess σ charge at CH_2 carbon	Excess σ charge over 6 carbon	Excess σ charge at halogen
$PhCH_2Cl$	0.15	-0.03	-5×10^{-4} e	489×10^{-4} e	653×10^{-4} e	-1415×10^{-4} e
$PhOCH_2Cl$	+0.41	-0.327	10609×10^{-4} e	2053×10^{-4} e	2.81×10^{-4} e	-1722×10^{-4} e

As the data indicates, the π-charge density in the ring is increased by 200 folds in $PhOCH_2Cl$ compared to $PhCH_2Cl$, it is noteworthy that this effect is more pronounced on σR than σI. Theoretical studies also confirm the above view.[318,319] It is quite possible, therefore, that in the cobaloximes (32-34) the conjugative effect of the heteroatom alone may be quite pronounced towards ring substitution and such an effect will follow the order NH > O > S. We observe in an independent experiment when an equimolar mixture of anisole and (33) is halogenated with one mole of bromine, anisole remains unreactive and is recovered back completely. Furthermore, the nature and yield of the products are identical to that from the reaction of bromine with (33). This clearly suggests that it is not only the heteroatom alone but the metallomethyl group also has a considerable effect on the activation of benzene ring.

(ii) The conjugative effect of metallomethyl group must be transmitted to the aromatic ring via the heteroatom and this will be more facile with a heteroatom having: a) low electronegativity, b) favourable π-symmetry, c) a combination of both. This seems justified from our results (with Br_2 and I_2) where the relative proportion of the organometallic product formed is more in (34) as compared to (32) and (33). The role of heteroatom therefore seems to be of two fold, (i) to activate the ring independently, and (ii) to transmit the conjugative effect of $-CH_2Co(III)$ group to the aromatic ring via its p-π orbitals.

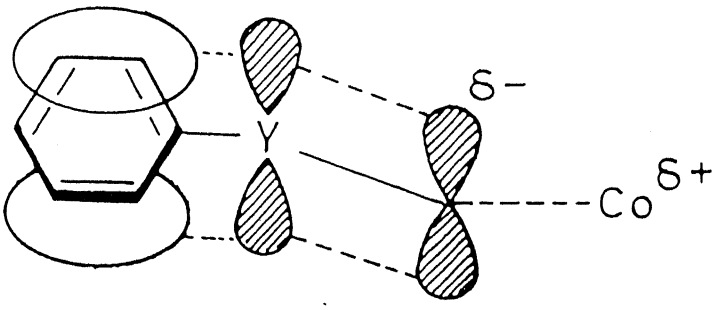
Furthermore, it is expected that geometrical considerations may also shed more light on the above π delocalization process. For example, the spatial position of $O-CH_2$ group attached to benzene ring is defined by the angle α (Ar-O-CH_2) and β (the angle by which the $-CH_2$ group is twisted out of the benzene plane).



The value of α remains fairly constant (118-120°) and is characteristic of an sp^2 oxygen atom, whereas the β value changes largely from compound to compound. Only a very low value of β (close to zero) places the oxygen pz orbital in perfect location for resonance interaction with the ring. This is likely to be the case in the present organocobaloxime systems.

There seems to be no doubt now that the effect of metallomethyl group $-CH_2Co(III)$ is definitely transmitted to the aromatic ring via the heteroatom and this effect results in the enhanced ring substitution product. At the same time, one must take into account the substituent effect of -YPh (Y = NH, O, S) on the $-CH_2Co(III)$ group which will lead to Co-C bond cleavage by the electrophile. A +I effect of -YPh will decrease the electron density at the Co-C bond whereas a -M effect should increase the same. In view of the following experimental observations: a) besides the organometallic product, the major organic product (95-103) formed in each case results from the direct Co-C bond cleavage of the parent cobaloxime; b) the ring halogenated organometallic products (86-94) and the organic products are formed simultaneously; c) the reactivities are much faster (<0.5 hour) in the present cobaloximes as compared to the similar reactions in benzyl cobaloximes (3 hours); it is clear that both the aromatic ring as well as the Co-C bond are sufficiently activated towards electrophilic attack and the extended $\sigma-\pi$ conjugation is mainly responsible for such

activation.



Extended σ-π Conjugation

However, it is very difficult to quantify the relative extent of activation at the aromatic ring and the α-carbon by the above process. In an earlier study from this laboratory,[320] a similar process has been demonstrated, i.e., while Co-C bond cleavage is the primary process in the halogenation of 2-furylmethyl and 2-thienylmethyl cobaloximes, exclusive substitution is observed in the corresponding 3-substituted derivatives. The results are best explained in terms of extended π-delocalization process.

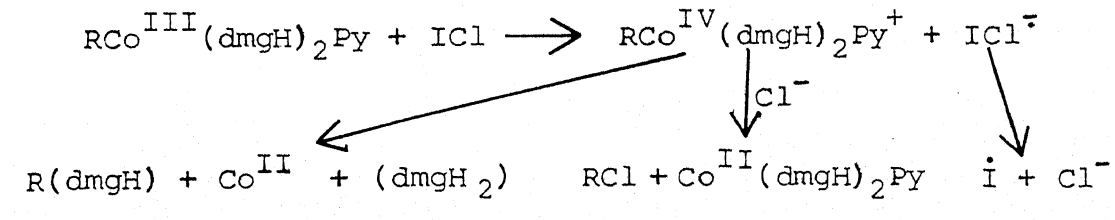
(iii) The following discussion will throw more light on the issue of an alternative mechanism. The effect of mechanism on the nature and yields of products should be taken into account. The nature of the products obtained suggests that the ring substitution and the cobalt-carbon bond cleavage occurs by an

electrophilic process. The latter seems to be the most prominent process occurring in all cases but in reactions with I_2 and ICl, the additional competitive mechanism come into play because of the prolonged reaction time. The formation of $PhYCH_2Cl$ in ICl reaction may arise by either or both oxidative dealkylation-mechanism (which involves preferential organic group transfer to the potentially negative chlorine atom of ICl molecule) and by the radical mechanism (which requires that both fragments of the ICl molecule must be equally active in attacking the leaving organic group). On the other hand the formation of small amount of O-organodimethylglyoxime mono ether points to the intermediate formation of $PhYCH_2Co^{IV}(dmgH)_2Py$ in solution which is unstable under reaction conditions and may undergo the following competitive reaction:

a) It may decompose to give ether products (105-107) by intramolecular transfer of organic group to the equatorial ligand by S_N2 or S_H2 mechanism.[168]

b) It may undergo nucleophilic displacement by Cl^- ion to give $PhYCH_2Cl$.

The following scheme may therefore outline the formation of the products:



R = $PhYCH_2$; (Y = O, S, NH)

$I^{\cdot}$ formed by decomposition of $ICl^{-\cdot}$ may undergo several reactions including oxidising more $RCo^{III}(dmgH)_2Py$ to $RCo^{IV}(dmgH)_2Py$, may act as a displacing radical and it may dimerise. The evolution of I_2 in the reaction medium supports the above scheme.

It is further observed that the following exchange reaction is occurring under the reaction conditions:

$$PhSCH_2I + ICl \longrightarrow PhSCH_2Cl + I_2$$

It seems, therefore certain that any amount of $PhSCH_2I$ formed either by direct electrophilic or by induced free radical cleavage of cobalt-carbon bond will undergo such exchange. It is, however, difficult to know the relative proportion of $PhSCH_2Cl$ coming from each one of these mechanisms.

It seems clear that the mechanism of iodination is different from that of chlorination and brominations in such systems. However, in view of the fact that Cl_2 and Br_2 are better oxidizing agents and poorer nucleophiles than I_2, one expects that the oxidative process is equally or more likely to occur in the former case. Since the oxidative process is not observed in chlorination and bromination, one may therefore consider the possibility that because of the prolonged reaction time in I_2 and ICl, the axial base, pyridine comes off and then one electron oxidation of the five coordinate species takes place. The high reactivity of the base off form has earlier been noted in cobaloximes[209] and cobalamins.[34] However, the rationale for

such high reactivity is difficult to draw at this stage. However, it will be taken up as a part of discussion in Chapter 3.

2.5 Mechanism of the Formation of Dimethylglyoxime mono ethers

We observe that benzyl ethers of dimethylglyoxime are the side products formed in many of the reactions described in this chapter. We have all along attributed its formation to the decomposition of the intermediate organocobalt(IV) species formed in solution. It is to be noted that similar one electron oxidation of a number of organocobalt(III) complexes has been achieved both chemically[138] and electrochemically[139] and the resulting oxidised form is so unstable at ambient temperature that it is detected only by cyclic voltametry and stop flow methods.[138,139] However, at lower temperatures (-30 to -80°C), life time is quite high[138,139] and many studies including ESR have been reported in literature.[138,149,321] In order to know the decomposition mechanism of the oxidised form an understanding of its structure and reactivity is necessary.

The structure of the oxidised form can be presented in terms of several limiting formulae differing in location of the unpaired electron and/or in valency of the metal:

$[R\text{-}Co^{IV}(L_4)B]^+$ $[\dot{R}\text{-}Co^{III}(L_4)B]^+$ $[\overset{+}{R}Co^{II}(L_4)B]$ $[R\text{-}Co^{III}(L_4^{\cdot+})B]$

A B C D

L_4 = bisbidentate or tetradentate ligand
B = axial base ligand

while A represents a complex with a usual Co-C covalent bond with +4 oxidation state on the metal, B and C can be viewed as complexes of organic free radical or carbenium ion with metal in +3 or +2 oxidation states, respectively. D is a cobalt(III) complex with a cation radical on the equatorial ligand (L_4).

Though structure D is predicted for organocobalt porphyrins,[321] structure A seems to be more likely for Schiff bases and organocobaloximes.[149] ESR spectra for organocobalt(IV) species reveals that the unpaired electron is localised predominantly on the metal.[148,276] The M.O. diagram is constructed by the 3 $d_{x^2-y^2}$ orbital, interaction of the filled metal 'd' orbitals with the antibonding π^* orbital of equatorial dimethylglyoximato ligands.[276]

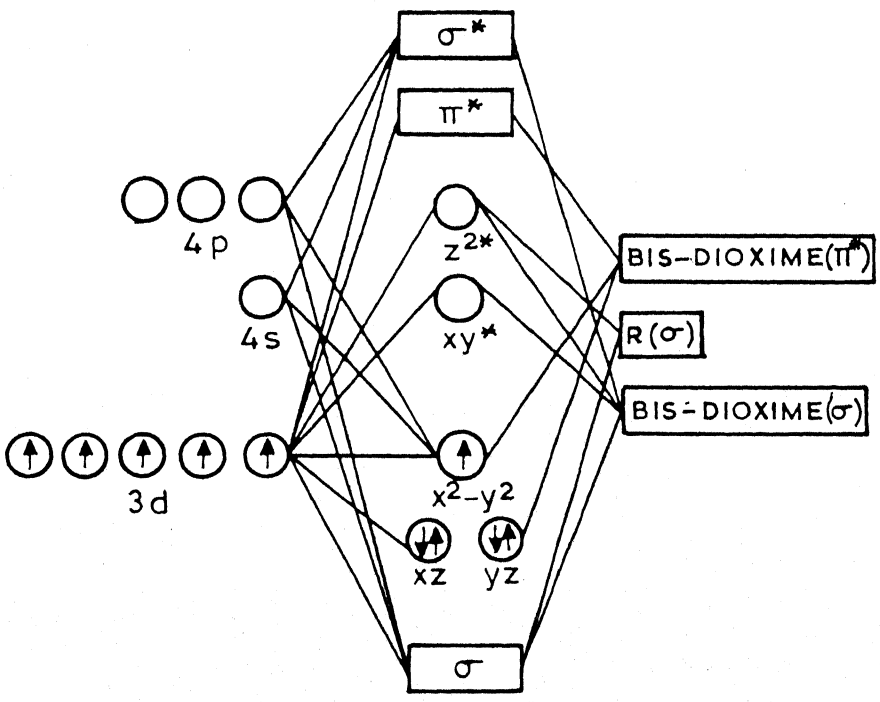


Fig. 5 MO diagram for organobis(dioximato) cobalt(IV). Reproduced from ref. 276.

Three routes are possible by which organocobalt(IV) species can decompose in solution.

(i) Homolytic splitting: The decomposition of $R(Co^{IV})$ in solution has been found to involve homolytic splitting of the metal-carbon bond.[141,322]

$$RCo^{IV}(L_4)B^+ \longrightarrow R^{\cdot} + Co^{III}(L_4)B^+$$

The possibility of such splitting can be postulated only from the formation of hydrocarbon products, i.e., RR (from self coupling of $R^{\cdot}$) and/or RH (from hydrogen abstraction by $R^{\cdot}$). The complete absence of bibenzyls and substituted toluenes in the present study rules out the possibility of such a process for the formation of the dimethylglyoxime mono ethers.

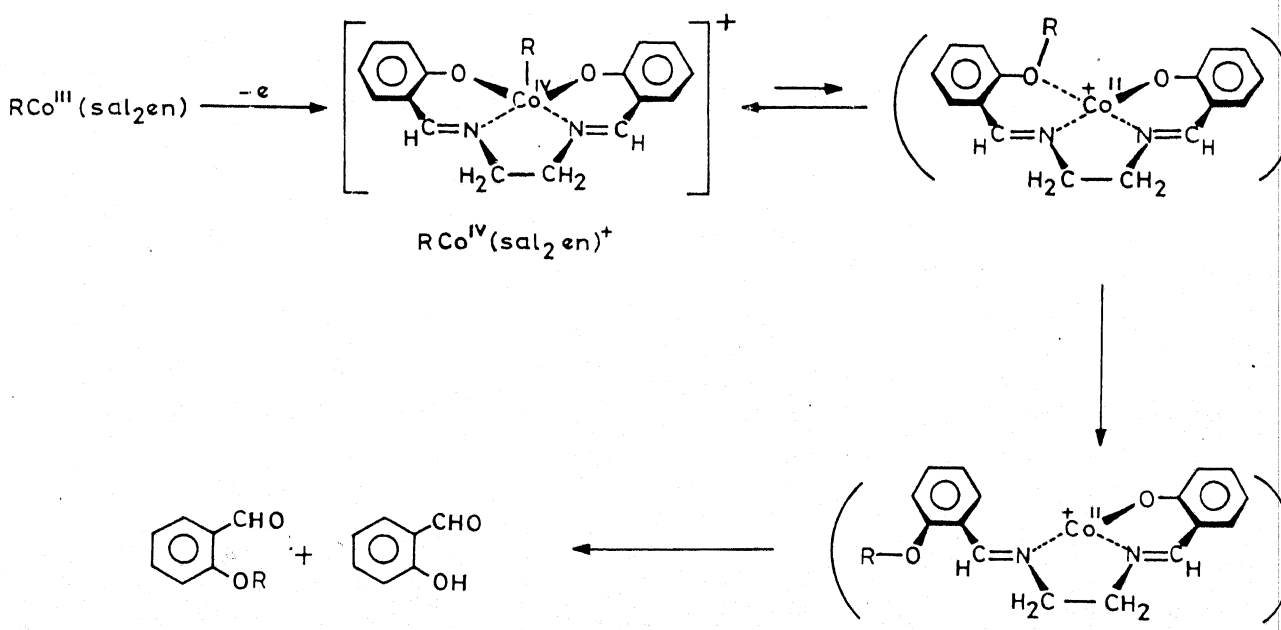
(ii) Nucleophilic substitution: The most characteristic reactions of organocobalt(IV) complexes are those of nucleophilic substitution at α carbon to metal:[139]

$$(R\text{-}Co^{IV})^+ + N\ddot{u} \longrightarrow R\text{-}Nu^+ + Co^{II}$$

For several Schiff's bases and dimethylglyoximato complexes, an S_N2 mechanism has been established with nucleophiles such as pyridine, water, Cl^- etc.[141] The attack of X^- (Cl^- and Br^-) in the present study is therefore expected. However, the nature and strength of the nucleophile plays an important role since there is always a competition between nucleophilic displacement

(a second order) and ether formation (probably a first order process). This point is clearly reflected in the example discussed earlier when bromination of $4\text{-}NO_2C_6H_4CH_2Co^{III}(dmgH)_2Py$ is carried out in the presence of Cl^-, the amount of $4\text{-}NO_2C_6H_4CH_2Cl$ formed is quite small because of the poor nucleophilicity of Cl^-.

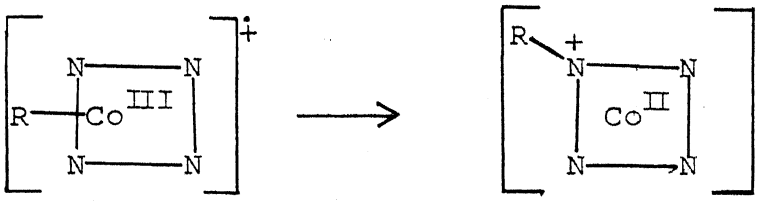
(iii) Intramolecular decomposition: Although most organocobalt(IV) complexes having Schiff's bases undergo nucleophilic displacement at carbon just like the corresponding dioximato complexes, however, the kinetic data[141] is consistent with S_N1 or S_Ni mechanism. A clear cut example of S_Ni mechanism involves transfer of R group from the metal to adjacent donor atom of the chelating ligand is given below:[145]



Scheme 2.6 Electrooxidation and decomposition of alkylcobalt(III)chelate with schiff base $(SalH)_2$ en[145]

This process is always in a direct competition with the S_N1 process.

Similar inner sphere transfer of R group from the metal to the adjacent donor atom also occurs in RCo^{IV} – porphyrin complexes.[142]



In view of the fact that S_Ni reactions are not uncommon in such complexes and the observed products in the present study are simply the alkylated products of the equatorial dimethylglyoxime ligand, it is therefore possible that such a S_Ni process in responsible for its formation. However, the transfer of R group may occur either as a nucleophilic displacement of Co^{II} by the dimethylglyoxime anion (S_N2)[323] or as a homolytic displacement of Co^{III} by the dimethylglyoxime radical (S_H2).[168] It is, however, very difficult to distinguish between these two processes, though S_H2 mechanism has been preferred by earlier workers.[153]

2.6 Summary

The study presented in this chapter reveals that electrophilic substitution in organocobaloximes in general, and benzylcobaloximes in particular, takes place with a high degree of complexity, especially when halogen is the electrophile. It is

not surprising that a number of mechanisms have been proposed for such a reaction and support for each mechanism has been accrued in the literature. However, no conclusive mechanism has been accepted so far. The story is complicated mainly because the nature of the end product(s) is same irrespective of the mechanism and it is very difficult to establish the relative contribution of each mechanism to the overall process. Earlier studies are restricted to benzylcobaloxime alone, where Co-C bond cleavage is the predominant process. Therefore, the transmission of the electronic effect of the metallomethyl group to activate the aromatic ring, has never been talked about.

Several factors need to be considered to understand the competitive ring halogenation versus Co-C bond cleavage. These include,

i) the nature and position of substituent in the aromatic ring,

ii) the one electron oxidation potential of the cobaloximes from (Co^{III}) to (Co^{IV}),

iii) the Co-C bond susceptibility towards homolysis and

iv) the nature of halogen molecule.

Inspite of all these odds, we have been able to achieve much information about the halogenation in benzylcobaloxime and its derivatives. Before presenting the highlights of the present study, it is very important to note that the conclusions are mainly drawn from final product distributions alone and no

kinetic measurements have been carried out. Besides, in reactions where encounter rate is approached, a slight variation in the rate of addition of the halogen, concentrations of substrate and halogen may change the relative proportion of the products.

2.7 Highlights

A brief account of the highlights of the present study is given below:

(1) A clear variation in mechanism with change in R group in 4-$RC_6H_4CH_2Co^{III}(dmgH)_2Py$ has been established, i.e., from direct electrophilic (R = Me, i-Pr, t-Bu) to oxidative dealkylation (R = H, Br, Cl, CN, CHO, COOH, NO_2) to electrophilic (R = OMe, $NHCOCH_3$, NMe_2). As said earlier, these are the major pathways operating, which may or may not have certain amount of contribution from other mechanisms.

(2) Chlorination and bromination certainly have a different mechanism from that of iodination, for example, 4-methoxybenzyl cobaloxime exclusively affords ring substituted toluene, 4-methoxy-2-halotoluene by a concerted electrophilic mechanism whereas the same cobaloxime with iodine forms 4-methoxybenzyliodide by a base off process as outlined by Okamoto.[209]

(3) We have been able to synthesize cobaloximes, for the first time, in which the aromatic ring is activated enough to undergo a preferential ring substitution by halogen as compared to Co-C bond cleavage. Therefore, we have been able to rationalize the substituent effect of organic group on to the Co-C bond and

is quite likely that its life time in solution is small and other reactions may be faster. (Ofcourse, this statement is true for those cobaloximes only, which are within the limits of oxidative potential by halogen.)

(5) Meta-substitution (Me, OMe) is much more effective in causing ring substitution as compared to the para-substitution.

(6) A slight change in the electron density at cobalt changes the course of reaction further. For example, 4-methylbenzylcobaloxime forms the corresponding halide by a direct electrophilic mechanism whereas the halogenation under protonated conditions proceedsvia oxidative dealkylation mechanism. Similar is the case with BF_2 bridged complexes.

Chapter 3

HETEROLYTIC CLEAVAGE OF COBALT-CARBON BOND BY THIOCYANOGEN

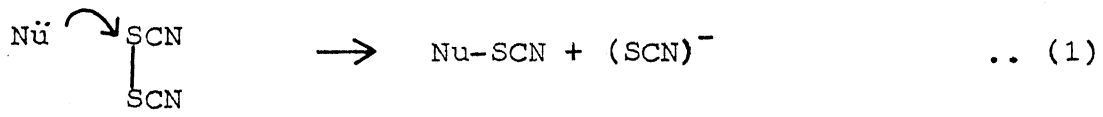
3.1 Aim of the Study

In the last chapter we have observed that although the reaction conditions do not allow the participation of a direct free radical pathway, but induced free radical process comes into play as a consequence of oxidative dealkylation. Since the final product i.e., the halide obtained is the same as that from the direct electrophilic or oxidative dealkylation process, the relative contribution of the induced free radical process can not be assessed. However, if one can choose an interhalogen/psuedohalogen which will afford different products from direct electrophilic and free radical pathways, it may, in principle, be possible to assess the relative contribution of the induced free radical process. Thiocyanogen should prove useful in this regards since both organothiocyanates and organoisothiocyanates will form in the free radical reaction.

3.2 Background

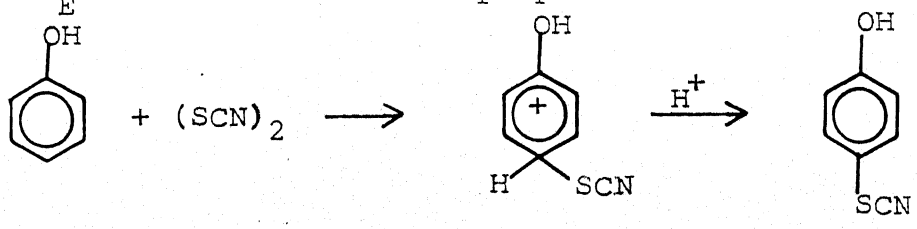
Thiocyanogen has been used as a useful reagent for the preparation of organic thiocyanates and much work to seek analogy with halogen for addition and subsitution reactions has been recorded in literature.[324,325] Recent work has supported both heterolytic as well as homolytic mechanism depending upon the substrates, conditions, solvents used.

Under heterolytic conditions, thiocyanogen acts as an electrophile and undergoes heterolytic S-S fission.



.. (1)

The reactivity of thiocyanogen falls between Br_2 and I_2[326,327] and its reactions are more facile with compounds having available π or p electrons. Several aromatic compounds including mononuclear and polynuclear hydrocarbons, phenols, amines etc. react with thiocyanogen in the presence of a catalyst.[325,328,329] Quantitative studies indicate that the substituent in the aromatic ring plays a very important role towards reaction rate, for example, electron donating substituents increase the rate of reaction whereas electron withdrawing groups decrease the rate. An S_E2 mechanism has been proposed for the following reaction.[325]



Similarly many heteroaromatic compounds react with thiocyanogen under very mild conditions.[325,330] Reactions with active methylene compounds, aliphatic amines, alkyl thiols, alkene, alkynes are also known. However, the reactions of thiocyanogen with metal complexes and organometallic compounds are rather few. The psuedoaromatic ring in copper complexes of porphyrins and metal acetylacetonates are readily thiocyanated. Organomercury and organozinc compounds give corresponding organothiocyanates along with new organometallic derivatives.[331,332]

$$R_2M + (SCN)_2 \longrightarrow RSCN + RMSCN$$

(M = Zn, Hg)

Heterolytic reactions of thiocyanogen are usually carried out either in dark or diffused light at 0-25°C. Such conditions, though satisfy most of the reactions, some conflicting reports of reaction rates, yields, products etc. have been reported in literature.[325] The major conflict has been the participation of homolytic process in the above reaction. This is particularly true for reactions of alkenes and alkynes.

The S-S bond of thiocyanogen is readily cleaved homolytically[333] by UV or visible light and the resulting thiocyanate radical is resonance stabilised:

$$\dot{S}\text{-}C{\equiv}N \longleftrightarrow S{=}C{=}\dot{N}$$

Thiocyanogen radical,[334] therefore, behaves like an acceptor radical and its reactions are restricted to systems having enhanced π electron density e.g., benzylic and allylic systems. The reactions are, however, slow compared to halogen atom. Many mechanisms including homolytic bimolecular radical chain mechanism have been reported in literature.[325]

The above discussion points to the versatile nature of thiocyanogen towards various electron rich organic and organometallic compounds. Moreover, as a psuedohalogen it offers an analogy with halogen except for its mild reactivity and low oxidising ability compared to halogen. Furthermore, this being a heteronuclear species having two reactive sites (S and N), offers a better probe to study the mechanistic feature from the point of view of products itself. In the previous chapter, a number of complexities were observed in reaction of halogens with benzyl cobaloximes. The study with thiocyanogen will help to gain further insight into the mechanism of Co-C cleavage.

3.3 Experimental

The general experimental procedure including details of solvents and gases, chromatography, physical measurements and instruments are same as those described earlier in Chapter 2, Sec. 2.2. The following additional features are noteworthy.

Low temperature (-10° to $-30^{\circ}C$) reaction was carried out in a specially designed glass apparatus attached to Julabo UC-40

model. Hydrogen chloride gas was generated by the treatment of concentrated hydrochloric acid with concentrated sulphuric acid.

Starting materials

Lead nitrate A.R. (B.D.H), bromine, chloroform, potassium thiocyanate, potassium phthalimide, dimethylformamide, hydrazine hydrate, hexamethylene tetramine, carbon disulphide, triethylamine, ethyl chloroformate, acetone were commercial materials and were distilled or recrystallised before use.

Organocobaloximes were synthesized according to the details given in Chapter 2, Sec. 2.2.2.

3.2.1 Synthesis of Organic and Inorganic Precursors

Preparation of thiocyanogen[335] (1)

Thiocyanogen is freshly prepared for each experiment and is immediately used.*

A solution of Br_2 (10% solution 4.3 mmol, in 10 ml $CHCl_3$) is added dropwise to a stirred suspension of lead thiocyanate** (4 fold excess, 5.6 g, 17.3 mmol in 20 ml chloroform).

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* A small percentage ($< 10\%$) is known to polymerise within the reaction time scale.

**Lead thiocyanate is prepared in bulk from potassium thiocyanate (19.4 g in 85 ml water) and lead(II) nitrate (33.1 g in 150 ml water) by the procedure of Gardner and Weinberger.[335] A dried and pure product is stored over calcium chloride in dark in the vacuum desiccator.

The suspension is further stirred for 20 minutes after the bromine colour is discharged. The solution is immediately used after filtration.

Reaction of thiocyanogen (1) with 4-$RC_6H_4CH_2Co^{III}(dmgH)_2Py$ (2-7; R = H, Me, OMe, Cl, CN, NO_2) and with $C_6H_5SCH_2Co^{III}(dmgH)_2Py$ (8)

Freshly prepared solution of thiocyanogen (4.3 mmol in 30 ml chloroform) is added dropwise to a dilute solution of organocobaloxime (2.1 mmol in 20 ml chloroform) in dark under nitrogen atmosphere. The course of reaction is monitored by TLC on silica gel G (Merck). After the reaction is over which usually takes 0.7-1.5 hours, the reaction mixture is filtered into a large excess of pentane. The solvent is removed in vacuum and the products are further separated on silica gel G or alumina (neutral) and/or by GLC. The inorganic product is also separated and characterised as (9).

Reaction of 4-chlorobenzyl cobaloxime (5) with thiocyanogen in sealed tube

A mixture of 4-chlorobenzyl cobaloxime (5) and thiocyanogen in 1:2 molar ratio in chloroform is taken in a tube which is sealed off under nitrogen. The tube is kept in a constant temperature bath at 90°C for 2 hours. The work-up procedure is same as above.

Reaction of 4-chlorobenzyl cobaloxime (5) with thiocyanogen under photochemical condition

A mixture of 4-chlorobenzyl cobaloxime (5) and thiocyanogen in 1:2 molar ratio in chloroform is irradiated with 2 x200 W tungsten lamps. The reaction is over within 0.5 hour. The reaction is worked up as outlined above.

Preparation of Authentic Samples

Benzyl thiocyanates, 4-$RC_6H_4CH_2SCN$ (R = H, Me, OMe, Cl, CN, NO_2)

All compounds are prepared by a general procedure of Bennett and Berry[336] as outlined below:

4-$RC_6H_4CH_2Br$* (R = H, Me, OMe, Cl, CN, NO_2) (20 mmol each) is taken in dry acetone (10ml) and is reacted with dry fused potassium thiocyanates (20 mmol in 20 ml acetone). The reaction mixture is stirred for a few hours, diluted with water and is extracted with solvent ether. Evaporation of the organic layer yields benzyl thiocyanate. The product is further distilled under vacuum or recrystallised from a mixture of solvents like cyclohexane/pentane, benzene/ether, toluene/ether and hexane/ether.

*All halides are synthesized by procedures outline in Chapter 2, Sec. 2.2.1.

Benzyl isothiocyanates,[337] 4-$RC_6H_4CH_2NCS$ (R = Cl, CN, NO_2)

A solution of 4-$RC_6H_4CH_2Br$ (30 mmol) and hexamethylenetetraamine (excess) in chloroform (50 ml) is heated to reflux for 4 hours. After cooling, the hexaminium salt, obtained after filtration is suspended in ethanol and hydrogen chloride gas is passed for 3 hours. The precipitated 4-$RC_6H_4CH_2NH_2$.HCl* is filtered and dried after recrystallization from water (yield: 60-70%).

A mixture of CS_2 (1.2 ml, 20 mmol) in chloroform (20 ml) is added dropwise over a period of 30 minutes to a stirred solution of 4-$RC_6H_4CH_2NH_2$.HCl (10 mmol) and triethylamine (20 mmol) in chloroform (40 ml) kept at -10°C. Ethyl chloroformate (30 mmol) is then added dropwise over a period of 20 minutes to the above solution (0°C) and the temperature of the mixture is raised to 17°C. Triethylamine (1 mmol in 30 ml chloroform) is added dropwise and the solution is further diluted with chloroform (100 ml). After washing the reaction mixture successively with 5% NaOH solution (2 x60 ml), 5% HCl (2 x60 ml) and water (2 x60 ml), the chloroform layer is dried over anhydrous $MgSO_4$. Evaporation of solvent and distillation under reduced pressure affords the corresponding 4-$RC_6H_4CH_2NCS$ in 60-75% yield.

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*4-$CNC_6H_4CH_2NH_2$.HCl is prepared from 4-$CNC_6H_4CH_2Br$ and potassium phthalemide in DMF by a procedure outline by McKay, et al.[337].

3.4 Results

The reaction of benzyl and 4-methyl benzyl cobaloxime (2 and 3, respectively) with thiocyanogen under dark and anaerobic condition form benzyl and 4-methyl benzyl thiocyanates as the exclusive organic products, respectively. However, reaction of 4-methoxy, 4-chloro, 4-cyano, 4-nitro benzyl cobaloximes (4-7) and phenyl methyl sulphide cobaloxime (8) with thiocyanogen under identical conditions form a mixture of products including thiocyanates, isothiocyanates, bibenzyls and benzyl ethers of dimethylglyoxime. The relative proportion of each product is given in Scheme 3.1 and their spectral characteristics and m.p./b.p. are given in Table 3.1.

The reaction of 4-chlorobenzyl cobaloxime (5) with thiocyanogen at -20°C forms exclusively 4-chlorobenzyl thiocyanate (14), whereas the same reaction carried out in a sealed tube at 90°C forms both 4-chlorobenzyl thiocyanate (14) and 4-chlorobenzyl isothiocyanate (15) in 85:15 ratio. Similarly, the reaction of (5) with thiocyanogen under photolytic conditions (irradiation by 400 W tungsten lamps) forms 4-chlorobenzyl thiocyanate, 4-chlorobenzyl isothiocyanate and 4-chlorobenzyl dimer in a ratio of 55:25:20, respectively. The only inorganic product isolated in all the reactions is sulphur bonded thiocyanato-bis(dimethylglyoximato)pyridinato cobalt(III) (9) as confirmed by i.r. spectroscopy.

Scheme 3.1: Organic Products from the Reaction of $RCo^{III}(dmgH)_2Py$ (2-8) with Thiocyanogen (1) in Chloroform

R	$(SCN)_2$	Organic Products (product No.)	Percent ratio[a]
$C_6H_5CH_2$ (2)	"	$C_6H_5CH_2SCN$ (10)	100
4-$MeC_6H_4CH_2$ (3)	"	4-$MeC_6H_4CH_2SCN$ (11)	100
4-$OMeC_6H_4CH_2$ (4)	"	4-$OMeC_6H_4CH_2SCN$ (12)	85
		4-$OMeC_6H_4CH_2$-ON=CMe-CMe=NOH (13)	15
4-$ClC_6H_4CH_2$ (5)	"	4-$ClC_6H_4CH_2SCN$ (14)	65
		4-$ClC_6H_4CH_2NCS$ (15)	15
		4-$ClC_6H_4CH_2$-ON=CMe-CMe=NOH (16)	20
4-$CNC_6H_4CH_2$ (6)	"	4-$CNC_6H_4CH_2SCN$ (17)	72
		4-$CNC_6H_4CH_2NCS$ (18)	8
		4-$CNC_6H_4CH_2$-$CH_2C_6H_4CN$-4 (19)	15
		4-$CNC_6H_4CH_2$-ON=CMe-CMe=NOH (20)	<5
4-$NO_2C_6H_4CH_2$ (7)	"	4-$NO_2C_6H_4CH_2SCN$ (21)	32
		4-$NO_2C_6H_4CH_2NCS$ (22)	27
		4-NO_2 C_6H_4 CH_2-$CH_2C_6H_4NO_2$-4 (23)	30
		4-$NO_2C_6H_4CH_2$-ON=CMe-CMe=NOH (24)	10
$C_6H_5SCH_2$ (8)	"	$C_6H_5SCH_2SCN$ (25)	88
		$C_6H_5SCH_2NCS$ (26)	7
		$C_6H_5SCH_2$-ON=CMe-CMe=NOH (27)	<5

a) From ^1H NMR only.

Table 3.1: Characteristics of Organic Products (10-27) obtained from the Reaction of Thiocyanogen (1) with Organocobaloximes (2-8) in Chloroform

Organic compound[a,b]	m.p./b.p.* (°C)	^{1}H NMR, $CDCl_3$ (TMS) δ(ppm) (200 MHz)		Mass: m/e (%)[e]
		Aromatic	CH_2	
1	2	3	4	5
(10)	42	7.34(m)	4.15(s)	149(14); 91(100)
(11)[c]	24	7.41(s)	4.19(s)	163(7); 105(100)
(12)[c]	82/0.5 mm*	6.85(m)[d]	3.97(s)	178(2); 121(100)
(14)	17	7.33(s)	4.10(s)	183, 185(10); 125, 127(100)
(15)	145/1 mm*	7.40[d]	4.75(s)	185, 183(18); 127, 125(100)
(17)	76	7.59, 7.84[d] (8 Hz)	4.22(s)	174(16); 116(100)
(18)	73	7.53, 7.78[d] (8 Hz)	4.68(s)	174(22); 116(100)
(19)	198	7.16-7.94(m)	3.36(s)	232(42); 116(100)
(21)	85	7.69, 8.37[d] (10 Hz)	4.25(s)	194(15); 136(100)
(22)	36	7.56, 8.34[d] (10 Hz)	4.91(s)	194(21); 136(100)
(23)	180.5	7.23, 8.1[d] (9 Hz)	3.08(s)	272(50); 136(100)

...contd.

Table 3.1 (contd.)

1	2	3	4	5
(25)	f	7.32(m)	4.58(s)	
(26)	f	7.32(m)	5.23(s)	

a) ^{1}H NMR spectra for compounds (13) ($CDCl_3$; TMS), δ(ppm): 6.85-7.3 (m, Ar); 5.1 (s, CH_2); 3.75 (s, OMe); 2.0, 2.06 (s, dmgH). Mass, m/e: 236 (10%); 121 (100%). m.p.: 72°C. Spectral data for (16), (20) and (24) appear in Chapter 2, page 107.

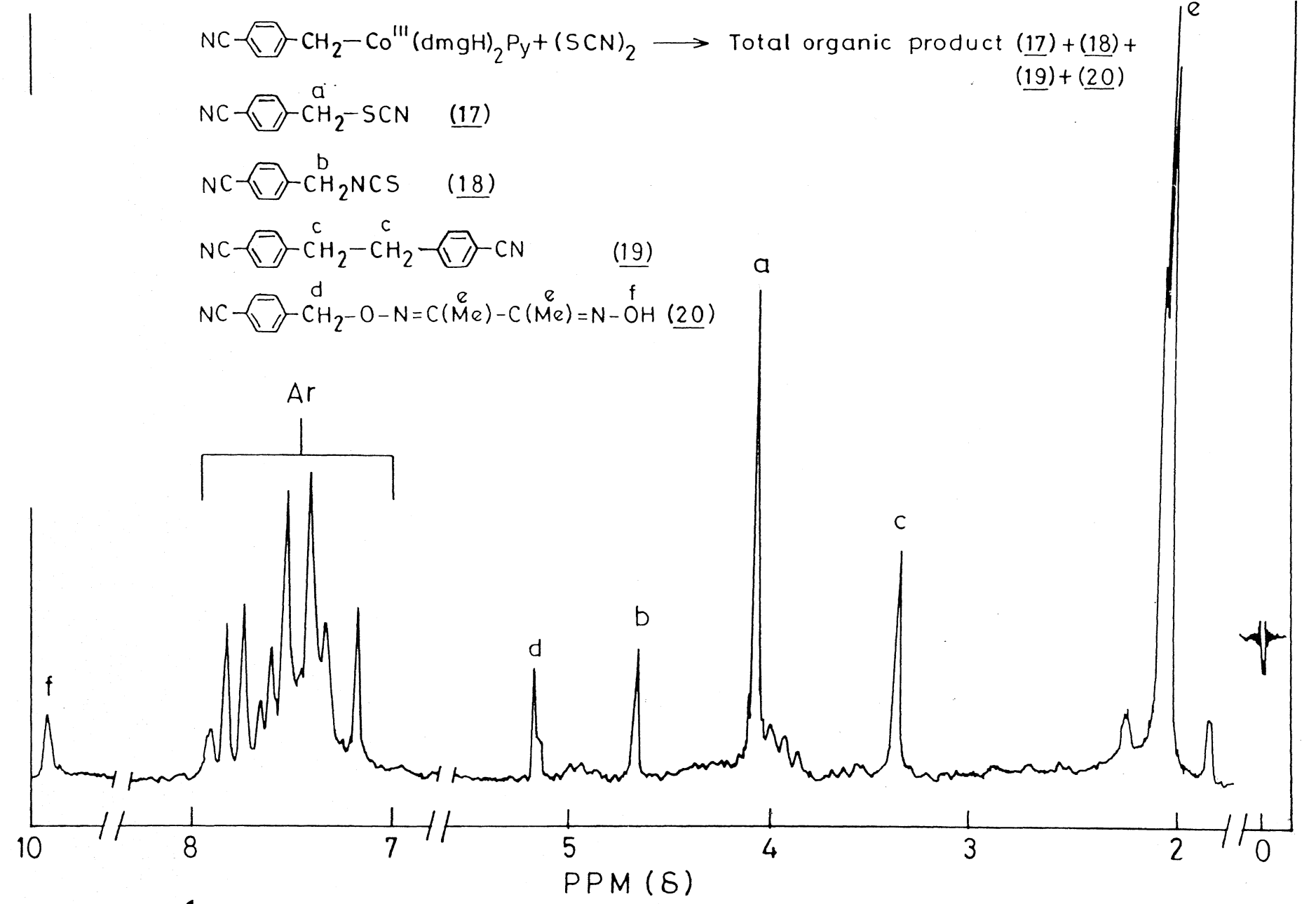
b) ν_{SCN}: 2150-2165 cm^{-1} and ν_{NCS}: 2070-2075 cm^{-1}.

c) For (11) methyl appears as singlet at 2.50 δ and for (12) methoxy appears as singlet at 3.68 δ .

d) A_2B_2 pattern is clearly observed and coupling constant is given in parentheses.

e) First value corresponds to $M^{+\cdot}$ peak and the second value corresponds to $4\text{-}RC_6H_4CH_2^{+}$.

f) Unstable, hence no other data obtained.

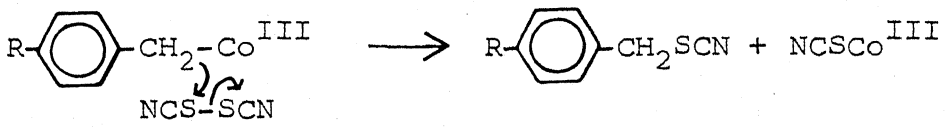


^{1}H NMR SPECTRUM (100 MHz) OF THE TOTAL ORGANIC PRODUCT.

3.5 Discussion

Thiocyanogen is known to react both by homolytic as well as heterolytic pathways. As reported in literature,[326,327] if the reactions are carried out in dark at ambient temperature and under inert atmosphere, the homolytic cleavage of S-S bond in thiocyanogen is largely inhibited. In the present study, the heterolytic pathway, therefore, should be the predominant process anticipated in all the reaction.*

Unlike halogenation study of Chapter 2, the reactions of organocobaloximes (2-8) with thiocyanogen (1) are much cleaner and provide moderate to good yields of corresponding benzyl thiocyanates, for example, the formation of benzyl thiocyanate (10) and 4-methylbenzyl thiocyanate (11) as exclusive organic products from the reaction of thiocyanogen with benzyl and 4-methyl benzyl cobaloximes (2 and 3, respectively) suggests that substitution at cobalt-carbon bond by thiocyanogen is the only process operating in these reactions.



*Since the heterolytic cleavage of thiocyanogen takes place in the presence of electron rich compounds having π electron density and organic thiocyanates are formed via kinetically controlled reactions, benzyl cobaloximes, therefore, besides a benzene ring, offer a π electron rich centre at α carbon bound to cobalt (due to σ-π conjugation). These cobaloximes, therefore, are ideal systems for study with thiocyanogen.

Since the aromatic ring is not activated enough, no substitution into the aromatic ring is observed.

In contrast, the reaction of thiocyanogen with 4-methoxy, 4-chloro, 4-cyano and 4-nitro benzyl cobaloximes (4-7) under similar conditions form a variety of products indicating that a mixture of mechanisms is operating in these reactions (see Scheme 3.1) for example, the formation of bibenzyls point to the participation of benzyl radicals in solution, the formation of benzyl ethers of dimethylglyoxime points to the intermediate formation of organocobalt(IV) in solution, and the formation of mixture of benzyl thiocyanates and isothiocyanates pointsto the free radical participation of thiocyanogen.

The formation of these products can be explained as follows: Since homolytic cleavage of S-S bond in thiocyanogen and unimolecular homolysis of Co-C bond in benzyl cobaloximes are highly unlikely processes under the reaction condition, a direct free radical mechanism seems to be out of question. Therefore, the bibenzyls and isothiocyanates must be formed by some kind of induced free radical reactions in solution.*

Furthermore, this is to be noted that thiocyanogen is a weak oxidising agent and its one electron reduction potential

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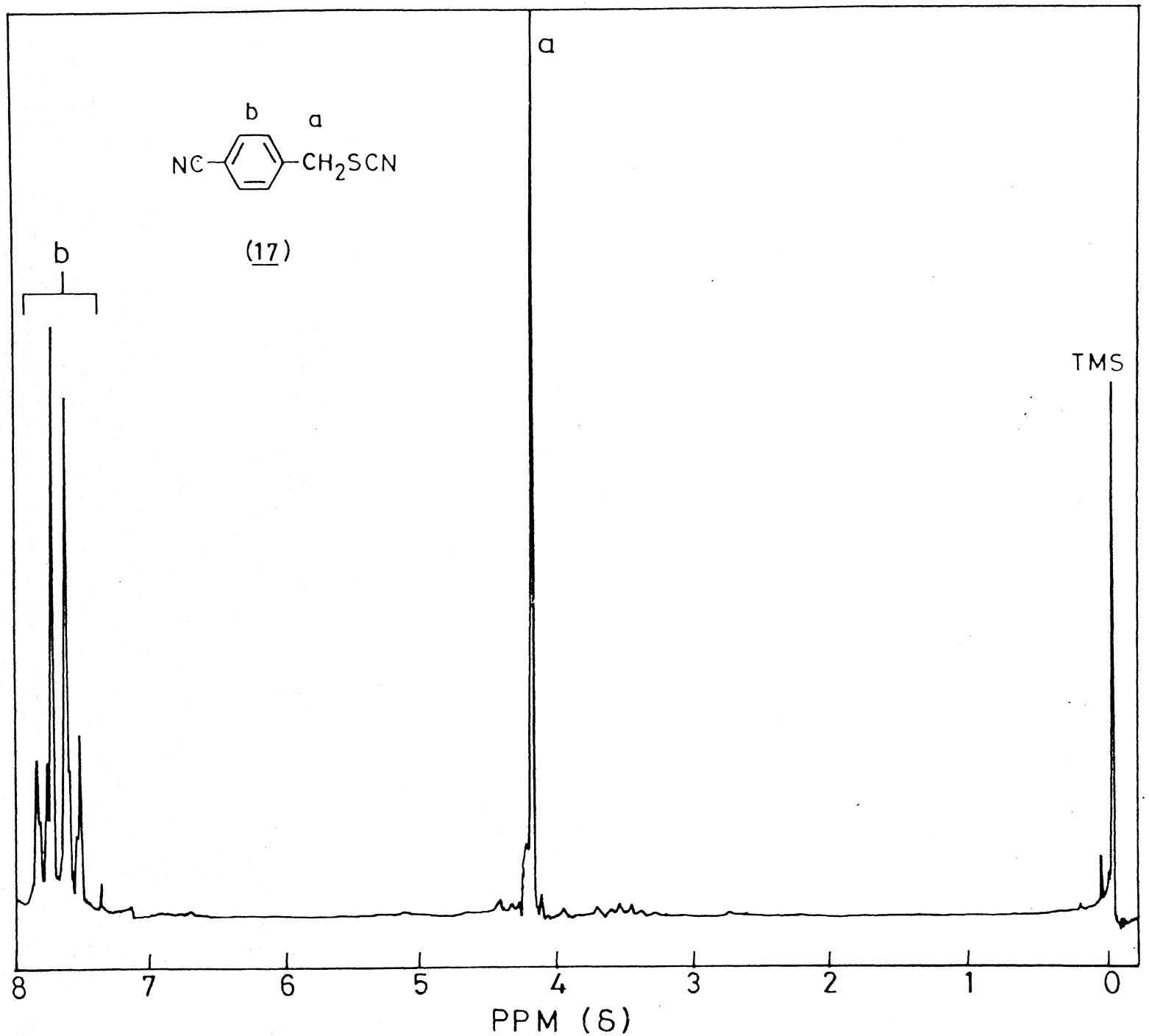
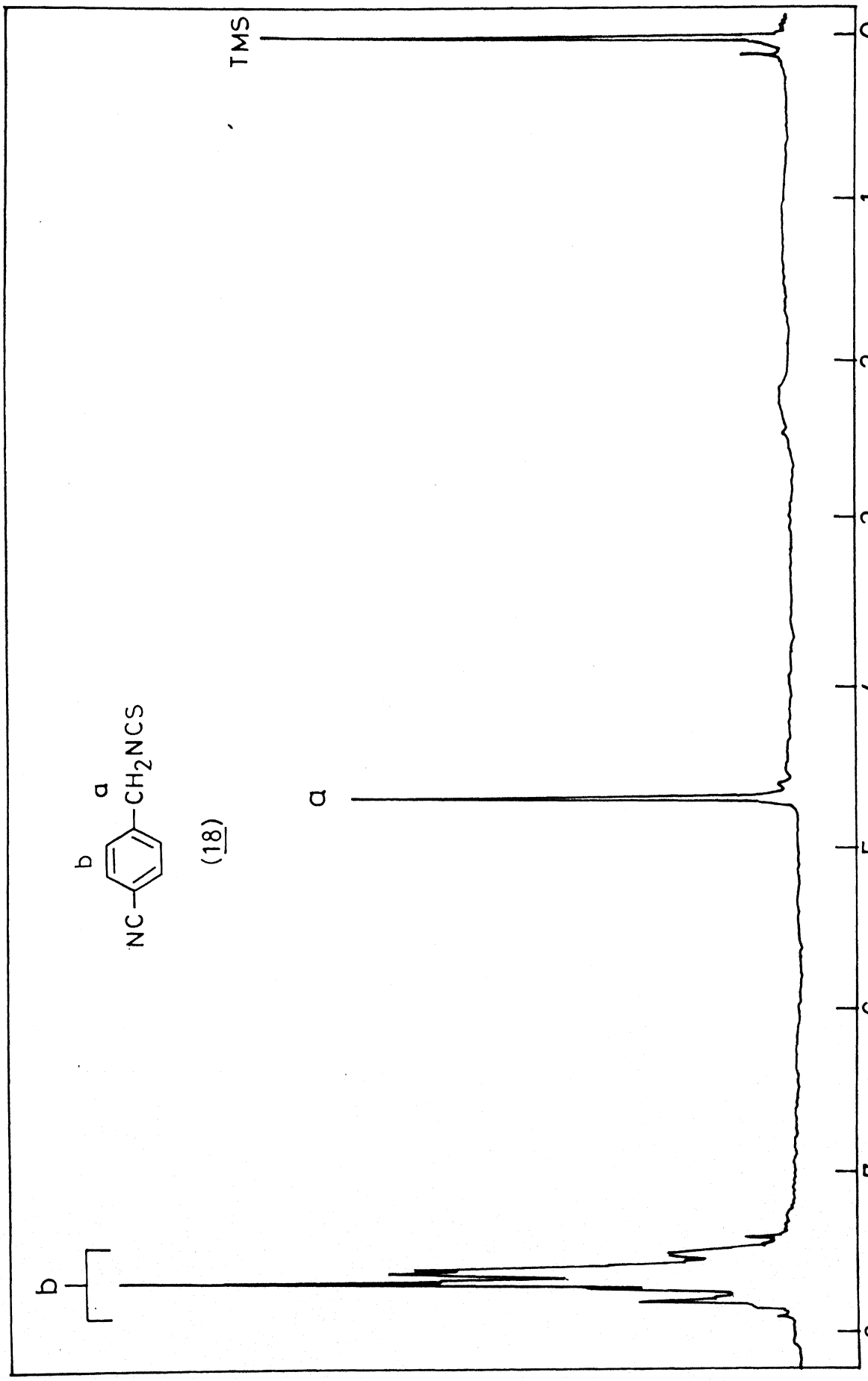
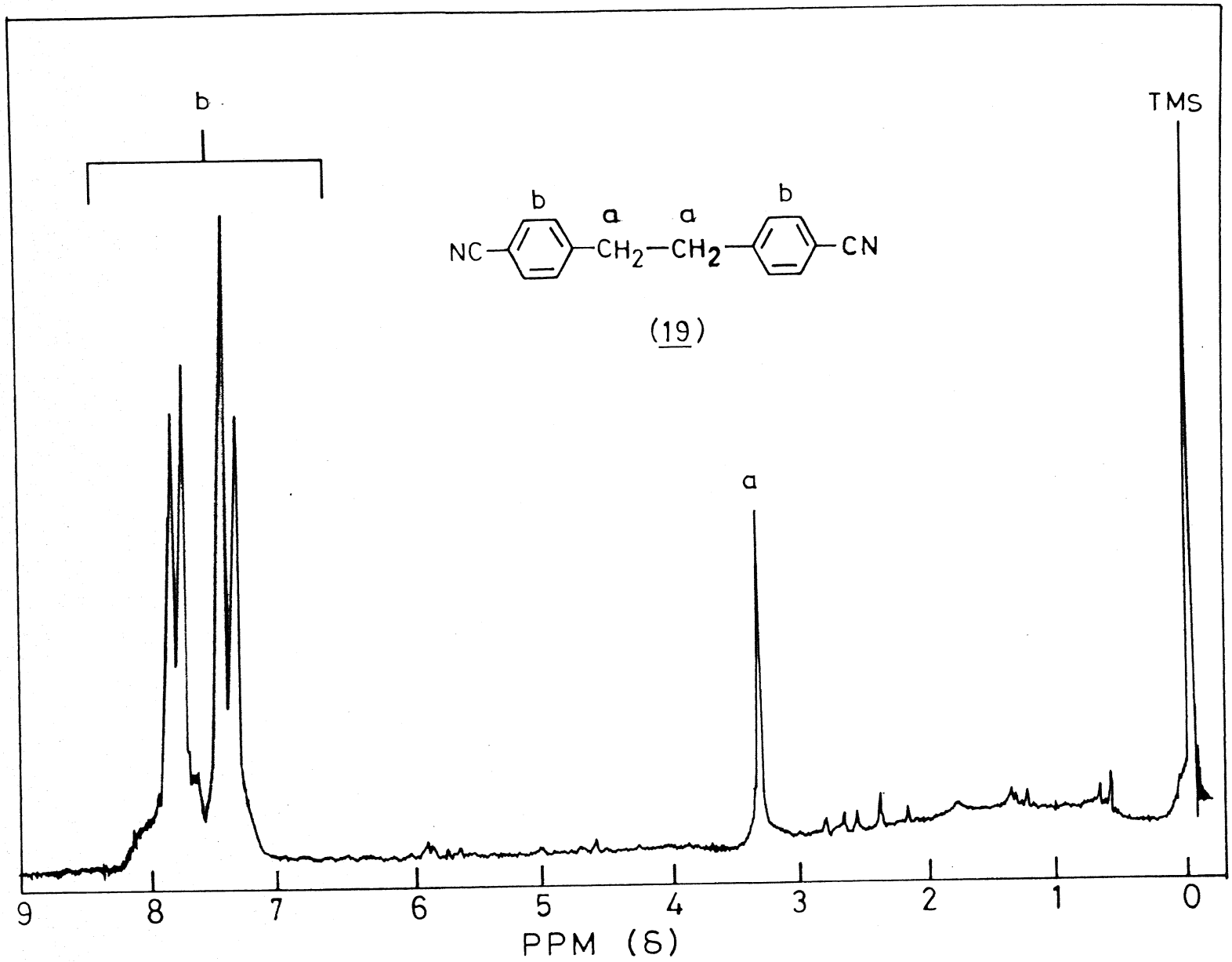
*Benzyl thiocyanates are known to isomerise to isothiocyanates at higher temperature in nucleophilic solvents, however, such a possibility is ruled out since we find that the product ratio before and after workup of reaction is same.



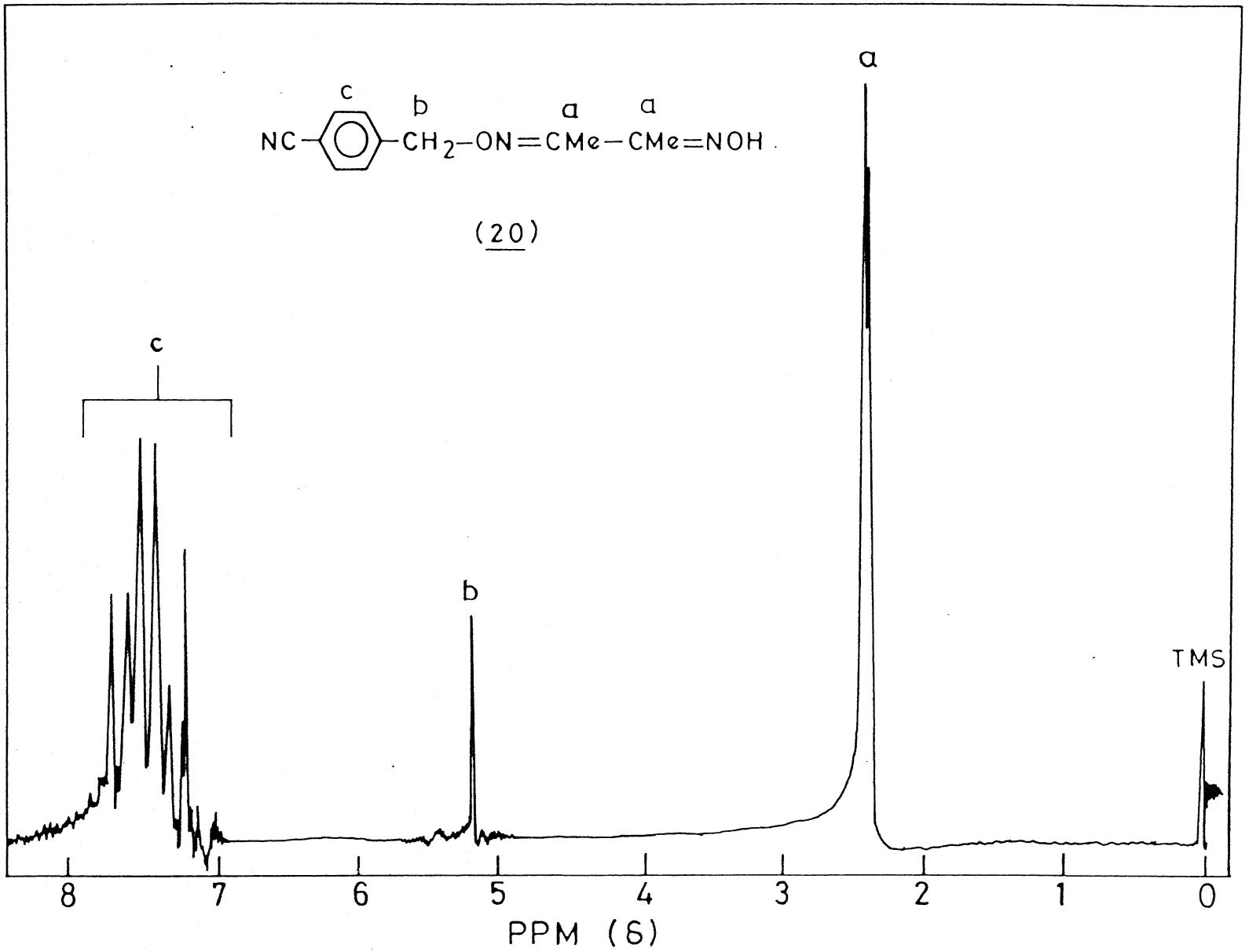
^1H NMR SPECTRUM (80 MHz) OF (17)



^1H NMR SPECTRUM (80MHz) OF (18)



^1H NMR SPECTRUM (90 MHz) OF (19)



^{1}H NMR SPECTRUM (90 MHz) OF (20)

(E_o = 0.783 V) is less than the one electron oxidation potential of benzylcobaloximes (> 0.80 V). It is, therefore, unlikely that thiocyanogen is able to oxidise the six coordinate benzyl cobaloximes. But the formation of benzyl ether of dimethylglyoxime definitely points to the intermediate formation of the oxidised species since such a product is a characteristic decomposition product of organocobalt(IV) species. (This point has been discussed in detail in Chapter 2). Since five coordinate benzyl cobaloximes are easily oxidisable even by weaker oxidising agents like iodine[209] ($I_2 \rightarrow I_2^{\cdot-}$, E_o = 0.54 V), it is quite likely that the oxidation is occurring on a five coordinate benzyl cobaloxime in the present case. This is further supported by our experimental observation that reaction of 4-chlorobenzyl cobaloxime (4) with thiocyanogen in the presence of pyridine, when six coordinate benzyl cobaloxime is the predominant species in solution, no oxidation takes place and 4-chlorobenzyl thiocyanate (14) is the exclusive organic product isolated.

The results can be explained by the following reaction Scheme 3.2 (page 191).

After one electron oxidation of the five coordinate $RCo^{III}(dmgH)_2$ (Eq.2), $(SCN)_2^{\cdot-}$ must break down to $(NCS)^-$ and $(NCS)^{\cdot}$ (Eq. 3). The fate of $(NCS)^-$ whose nucleophilic reactivity[339] is better than Cl^- will be to undergo bimolecular nucleophilic attack at the organocobalt(IV) species to form benzyl

Scheme 3.2

$$RCo^{III}(dmgH)_2Py \underset{+Py}{\overset{-Py}{\rightleftharpoons}} RCo^{III}(dmgH)_2 \quad .. (1)$$

$$RCo^{III}(dmgH)_2 + (SCN)_2 \longrightarrow [RCo^{IV}(dmgH)_2]^+ + (SCN)_2^{\cdot-} \quad .. (2)$$

$$(SCN)_2^{\cdot-} \longrightarrow (SCN)^- + (NCS)^{\cdot} \quad .. (3)$$

$$[RCo^{IV}(dmgH)_2]^+ \xrightarrow[(SCN)^-]{a} RSCN \text{ (or RNCS)} + Co^{II}(dmgH)_2$$
$$\xrightarrow{b} R\text{-}ON{=}CMe\text{-}CMe{=}NOH \quad .. (4)$$

$$RCo^{III}(dmgH)_2 \xrightarrow{(NCS)^{\cdot}} [RCo^{IV}(dmgH)_2SCN] \quad .. (5)$$

$$[RCo^{IV}(dmgH)_2SCN] \longrightarrow \dot{R} + Co^{III}(dmgH)_2SCN \quad .. (6)$$

$$\dot{R} \xrightarrow[a]{\dot{R}} R\text{-}R$$
$$\xrightarrow[b]{(NCS)^{\cdot}} RSCN \text{ or } RNCS \quad .. (7)$$

$$RCo^{III}(dmgH)_2Py \xrightarrow{(NCS)^{\cdot}} RSCN \text{ or } RNCS + Co^{II}(dmgH)_2Py \quad .. (8)$$

$$Co^{II}(dmgH)_2Py + (SCN)_2 \longrightarrow NCSCo^{III}(dmgH)_2Py + (SCN)^{\cdot} \quad .. (9)$$

$$Co^{II}(dmgH)_2 + (SCN)_2 \longrightarrow NCSCo^{III}(dmgH)_2 + (SCN)^{\cdot}$$
$$\downarrow Py$$
$$NCSCo^{III}(dmgH)_2Py \quad .. (10)$$

thiocyanate* (Eq. 4a). However, the fate of $(NCS)^{\cdot}$ is very difficult to assess since it can undergo many reactions including a homolytic displacement at carbon in $RCo^{III}(dmgH)_2Py$ (Eq. 8) to form both benzyl thiocyanate and isothiocyanate,** it may oxidise more of $RCo^{III}(dmgH)_2$ to form $RCo^{IV}(dmgH)_2NCS$ (Eq. 5) which will undergo unimolecular homolysis to form $\dot{R}$ and $Co^{III}(dmgH)_2NCS$ (Eq. 6). $\dot{R}$ may dimerise to form R-R (Eq. 7a) or it may couple with SCN to form RNCS (Eq. 7b).‡ The formation of R-R and RNCS products in the reactions supports the later view. Like halogenation studies (Chapter 2), it is very difficult to assess the relative contribution of each factor towards the formation of total benzyl thiocyanate. However, it is beyond doubt that oxidative dealkylation occurs only on the five coordinate species and it definitely induces free radical reactions as well. This supports the similar observation made in the halogenation study.

It is surprising to find that the only inorganic product obtained is sulphur bonded $NSCo^{III}(dmgH)_2Py$, though one should expect the formation of a mixture of both nitrogen bonded as well as sulphur bonded cobaloxime.[340]

*In NCS^-, the negative charge resides more on sulphur hence the thiocyanate formation should be the exclusive product. However, in the reaction of KSCN with alkyl halides a little amount of alkyl isothiocyanates has been observed as a side product which arises by a competing kinetically controlled reactions of N and S ends of thiocyanato nucleophile.

**This has been proved by an independent reaction when 4-chlorobenzyl cobaloxime with thiocyanogen under irradiation at room temperature form 4-chlorobenzyl thiocyanate and 4-chlorobenzyl isothiocyanate (see Experimental Section).

‡This is the only route by which R-R can be formed.

SCOPE FOR FUTURE WORK

The study presented in the foregoing chapters clearly reveals that the reactions of benzyl cobaloximes with halogens and pseudohalogens are quite complex in nature. These complexities arise mainly because of simultaneous participation of a number of mechanisms. The preference of one mechanism over the other is guided by many factors like substrate organocobaloximes, electrophilic reagents and the reaction conditions. Therefore, it becomes a very difficult task to precisly pinpoint the relative contribution of each one of these mechanisms. For a better understanding more number of electrophiles under diverse reaction conditions need to be investigated. Furthermore to prove conclusively the nature of intermediate(s) involved, accurate kinetic studies are necessary. Lastly, the direct studies on vitamin B_{12} coenzyme itself should be taken up in the light of the overall information from these model studies.

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VITAE

Born on July 1st, 1962 at Ayodhya, Uttar Pradesh, the author had his earlier education at Government Inter College, Bareilly. He took his B.Sc. degree in 1980 at Christian College, Lucknow and M.Sc. degree at Department of Chemistry, University of Lucknow in 1982. He joined the Ph.D. programme of the Department of Chemistry, I.I.T., Kanpur in July 1982 and is presently continuing as a Senior Research Scholar in the same department.